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LACunar Intervention Trial 3

Submission date
29/10/2024

Recruitment status
Recruiting

Registration date
24/12/2024

Overall study status
Ongoing

Last Edited
28/01/2025

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Having a lacunar stroke increases the risk of another stroke, dementia, and loss of independence. A quarter of strokes, called lacunar strokes, are caused by disease of the smallest blood vessels in the brain. Lacunar strokes occur when small blood vessels deep within the brain become damaged and do not supply oxygen and nutrients well. The blood supply to part of the brain is interrupted. When there is an interruption in blood supply to part of the brain, the lacunar stroke happens.
It affects about 35000 people per year in the UK. This ‘small vessel disease’ can also cause problems with thinking, balance and walking and can sometimes lead to dementia. There are no treatments yet to help the small blood vessels work better. As a result, damage to the brain may continue to build up.
We have found two drugs that may reduce damage to the small blood vessels in the brain and, therefore, could prevent strokes and thinking problems caused by small vessel disease.
One drug, called cilostazol, is most used in the UK to treat problems with the blood supply to the legs but is used to prevent more strokes from happening in many other countries.
The other drug, called isosorbide mononitrate, is commonly used worldwide, including in the UK, to treat angina (chest pains caused by poor blood supply to the heart).
A network of 60 UK hospitals will identify patients after lacunar stroke and invite them to participate. LACI-3 will need 1300 participants to confirm whether isosorbide mononitrate and cilostazol, taken alone or together, reduce the risk of another stroke, dementia, and loss of independence. Participants will take study tablets for 18 months, during which we will collect information on health, cognition, and quality of life.

Who can participate?
Adults aged 30 years and older who have had a lacunar stroke.

What does the study involve?
Participants will be randomly assigned to one of the four groups:
1. They may be given cilostazol only.
2. They may be given isosorbide mononitrate only.
3. Both cilostazol and isosorbide mononitrate will be given.
4. Neither cilostazol nor isosorbide mononitrate is given.

Everyone gets guideline standard medical care.
Participants will be taking part in LACI-3 for 18 months and follow up five times during their treatment by phone and post.

What are the possible benefits and risks of participating?
The findings of LACI-3 will be used in everyday clinical practice in the NHS to care for people with lacunar stroke and prevent future stroke and dementia before symptoms develop.
The trial has been designed to minimise the participants' burden, and the trial materials allow them to contact the trial hospital, central office, or an independent advisor at any time should they need advice. The potential side effects of the study drugs are well-known, and the hospital research team will explain the risks to the participants. Based on the results from the LACI1/2 trials, the study drugs were well-tolerated and safe.
The follow-up will be delivered remotely by phone and post at regular intervals, and participants will be asked about any new drug symptoms or health problems. To minimise travel to the hospital site, they will receive a re-supply of the study drug(s) by post or courier. Participants may find completing the follow-up questionnaires inconvenient; however, the research teams will use each follow-up visit to monitor participants' health, including blood pressure checks. Participants will also be informed that they can ask someone to complete the follow-ups on their behalf if they have difficulties in writing or visual impairment. Participants will have a chance to complete a postal questionnaire by phone if preferred.

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

When is the study starting and how long is it expected to run for?
October 2024 to December 2028

Who is funding the study?
National Institute for Health and Care Research (NIHR) Health Technology Assessment (UK)

Who is the main contact?
laci-3@ed.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

Contact name
Prof Joanna Wardlaw

ORCID ID
https://orcid.org/0000-0002-9812-6642

Contact details
Centre for Clinical Brain Sciences
First floor
Chancellor’s Building
49 Little France Crescent
Edinburgh
United Kingdom

EH16 4SB
-
Joanna.Wardlaw@ed.ac.uk

Type(s)
Public

Contact name
Ms Kasia Adamczuk

ORCID ID
https://orcid.org/0009-0009-5158-6818

Contact details
Centre for Clinical Brain Sciences (CCBS)
University of Edinburgh
Chancellor's Building Room
49 Little France Crescent
Edinburgh
United Kingdom
EH16 4SB
-
laci-3@ed.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1008629

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
AC24127

Study information

Scientific Title
The LACunar Intervention Trial 3 (LACI-3). Assessment of efficacy and safety of cilostazol and isosorbide mononitrate to prevent adverse outcomes in patients with cerebral small vessel disease (lacunar) ischaemic stroke.

Acronym
LACI-3

Study objectives

Primary research question:
For adults surviving lacunar ischaemic stroke, does a policy of starting a drug called cilostazol or a drug called isosorbide mononitrate or starting both of those drugs result in a reduction of problems with memory and thinking compared to continuing routine stroke prevention therapy only?

The secondary objectives of the LACI-3 study are to determine if two tested drugs called cilostazol and isosorbide mononitrate, taken alone or together:
1. Reduces dependency
2. Helps prevent small vessel disease (problems in tiny blood vessels deep in the brain) from causing another stroke, heart attack or death
3. Improves mood
4. Improves quality of life
5. Reduces use of NHS or social care services
6. If they can be used safely in patients with a lacunar stroke
7. And if patients can take them over several years

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 20/01/2025, Scotland B Research Ethics Committee (Waverley Gate, 2 - 4 Waterloo Place , Edinburgh, EH1 3EG, United Kingdom; +44 7814609032; Manx.Neill@nhslothian.scot.nhs.uk), ref: 24/SS/0095

Study design
Prospective randomized open-label blinded endpoint factorial trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Lacunar (small vessel) ischaemic stroke

Interventions
The intervention involves random allocation to one of the four treatment groups, in addition to the guideline standard care after lacunar ischaemic stroke, using an electronic randomisation system:
1. Isosorbide mononitrate (ISMN) oral:
1.1. Slow release 50 mg once daily or
1.2. Non-slow-release 20 or 25 mg twice daily
2. Cilostazol 100 mg oral twice daily
3. Both ISMN and cilostazol - same doses as above
4. Neither ISMN nor cilostazol

A target dose of isosorbide mononitrate is 40-60 mg daily. If a slow-release ISMN is not available, the non-slow-release tablets may be used.

The IMP is defined by the active substance only, therefore all authorised brands may be used. There is no placebo. The comparator will be a standard care alone including guideline stroke secondary prevention prescribed post-stroke as per national guidelines.

The trial treatment period is 18 months.

There are five follow-up timepoints after randomisation:
1. 1–2-week follow-up by phone
2. 3–4-week follow-up by phone
3. 6-month follow-up by post and phone
4. 12-month follow-up by post and phone
5. 18-month follow-up by post and phone

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Cognitive impairment after lacunar ischaemic stroke will be evaluated at 18 months after randomisation using the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) scale operationalised, a 7-level ordinal cognitive impairment scale using subscores of the Telephone Montreal Cognitive Assessment (tMOCA), Telephone Interview for Cognitive Status (TICS), animal naming, clinical dementia diagnosis measured at 6, 12 and 18 months.

Key secondary outcome(s))
Secondary outcome measures:
The secondary outcomes will be evaluated at 18 months after randomisation:
1. Dependency (defined as mRS>2) is measured using a Modified Rankin Score at 6, 12 and 18 months
2. Cognitive impairment or dementia are measured at 6, 12 and 18 months using:
2.1. Telephone-Montreal Cognitive Assessment (t-MOCA)
2.2. Telephone Interview for Cognitive Status (TICS)
2.3. Concentration (from Mini-Mental State Examination [MMSE])
2.4. Animal naming
3. Clinical outcomes are measured using postal/telephone questionnaires and medical notes during 18 months after randomisation:
3.1. Recurrent ischaemic stroke or transient ischaemic Attack (TIA) or haemorrhagic stroke
3.2. Fatal or non-fatal myocardial infarction (MI)
3.3. Death, due to vascular and any cause
4. Safety outcomes are measured using reported Serious Adverse Events (SAEs) during 18 months after randomisation
5. IMP symptoms are measured using telephone/postal questionnaires at 1-2 weeks, 3-4 weeks, and 6, 12 and 18 months
6. Quality of life is measured using:
6.1. Stroke Impact Scale (individual domains and global) postal questionnaire at 6, 12 and 18 months

6.2. EQ5D-5L, EQ-VAS of the EuroQol paper questionnaire at randomisation and 18 months
6.3. Mood is measured using the ZUNG depression rating scale at 6, 12 and 18 months
6.4. Composite of recurrent stroke or TIA, MI, death, dependency (mRS>2), cognitive impairment at 18 months after randomisation
6.5. Global Clinical Outcome of recurrent stroke or TIA, MI, death, mRS>2, cognitive impairment, QoL, mood (ZUNG) at 18 months after randomisation
6.6. Health economic usage using a postal questionnaire is measured 18 months after randomisation

Tertiary outcome measures:
Blood pressure measures will be evaluated at 18 months after randomisation using blood pressure measurements made by participants or available from GP or hospital medical records as a part of the routine stroke prevention therapy at randomisation, 1-2 weeks, 3-4 weeks and at 6, 12 and 18 months.

Completion date
31/12/2028

Eligibility

Key inclusion criteria
1. Age ≥30 years
2. Clinical stroke syndrome compatible with a lacunar stroke and brain imaging (MRI preferred but CT allowed) at the time of the stroke shows a relevant recent small subcortical infarct, or if no relevant infarct then no other explanation for symptoms is seen
3. Genetic forms of SVD (e.g. CADASIL) may be included if they present with a lacunar stroke
4. Capacity to give consent in the opinion of the PI or any delegated member of the research team

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
30 years

Sex
All

Key exclusion criteria
General Exclusion Criteria:
1. Less than 24 hours since onset of the lacunar stroke or patient on dual antiplatelet drugs
2. Stroke mechanism with definite treatment indication (e.g. cardioembolism, ipsilateral carotid stenosis)
3. Other explanation for the lacunar stroke symptoms (i.e., recent cortical infarct, haemorrhage

or tumour)
4. Other active neurological disease (e.g., brain tumour, multiple sclerosis, recurrent seizures, neurodevelopmental disorder - well-controlled epilepsy present prior to the lacunar stroke, a single seizure at onset of the stroke, or provoked seizure, is not an exclusion)
5. Contraindication to both trial drugs in section 4.3 of the SPCs (patients with a contraindication to one trial drug may still be randomised to the other trial drug)
6. Indication for either trial drug (patient already prescribed one trial drug may still be randomised to the other trial drug)
7. Dependent (mRS>2)
8. Clinical diagnosis of dementia
9. Planned surgery during the trial period including carotid endarterectomy. Note 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
10. Unable to swallow
11. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100mmHg
12. History of drug overdose or attempted suicide
13. Unlikely to be available for follow-up at 18 months
14. 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
15. Pregnant, breast-feeding, or of child-bearing potential and not using highly effective contraception
16. Renal impairment (creatinine clearance <25 ml/min)
17. Hepatic impairment
18. Currently prescribed dual antiplatelet treatment (single antiplatelet is not an exclusion); patients can be randomised into the trial once the 28-day period of dual antiplatelet for guideline secondary prevention following the acute lacunar ischaemic stroke has completed
19. Previously enrolled in LACI-3
20. Enrolled in a study that precludes co-enrolment with LACI-3

Cilostazol Exclusion Criteria (still allows randomisation to ISMN):
1. Definite indication for (i.e., already prescribed) Cilostazol, or definite contraindication to Cilostazol as per SPCs section 6.1.8.
2. Prohibited medications to Cilostazol (see sections 4.5 of the appended SPCs and protocol section 6.7.3)
3. Active cardiac disease (atrial fibrillation, myocardial infarction in past 6 months, active angina, symptomatic cardiac failure)
4. 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)

ISMN Exclusion Criteria (still allows randomisation to Cilostazol):
1. Definite indication for (i.e., already prescribed) ISMN, or definite contraindication to ISMN as per SPCs
2. Prohibited medications to ISMN (see sections 4.5 of the appended SPCs and protocol section 6.7.3)

Date of first enrolment
03/03/2025

Date of final enrolment

30/06/2027

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Royal Infirmary of Edinburgh
Centre for Clinical Brain Sciences
Chancellor's Building
49 Little France Crescent
Lothian
United Kingdom
EH16 4SB

Sponsor information

Organisation
University of Edinburgh

ROR
https://ror.org/01nrxwf90

Organisation
NHS Lothian

ROR
https://ror.org/03q82t418

Funder(s)

Funder type

Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Professor Joanna Wardlaw (Joanna.Wardlaw@ed.ac.uk). Researchers may apply to use a de-identified version of the dataset for prospective individual patient data meta-analysis and a data dictionary after 1 year of the publication of the results. A LACI-3 data-sharing committee will assess the written proposals and decide whether data use is appropriate. A data-sharing agreement must be in place before any data sharing.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes