# In patients with a "small vessel" stroke, can the risk of further strokes and problems with thinking, memory or mobility be reduced?

Submission date Recruitment status [X] Prospectively registered 02/10/2017 No longer recruiting [X] Protocol [X] Statistical analysis plan Overall study status Registration date 09/10/2017 Completed [X] Results [ ] Individual participant data **Last Edited** Condition category 05/11/2024 Circulatory System

### Plain English summary of protocol

Current plain English summary as of 14/02/2020:

Background and study aims

About 35,000 people each year in the UK have a type of stroke, called 'lacunar' or 'small vessel' stroke, which is different to other common types of stroke and for which there is no proven treatment. Small vessel stroke may be caused by damage to the lining of the tiny blood vessels deep inside the brain that stops them functioning normally. This not only causes stroke but, perhaps more importantly, causes problems with thinking and walking, possibly causing up to 45% of all dementias either on its own, or mixed with Alzheimer's disease (about 350,000 patients in the UK). Some drugs that are commonly used in other blood vessel diseases may help improve small vessel function and prevent worsening of brain damage. One drug (cilostazol) has been tested in patients with stroke in the Asia Pacific countries but not on dementia; the other drug (isosorbide mononitrate) is widely used in the UK for heart disease but not stroke. The aim of this study is to test if the study methods are practical so that patients and trial centres can follow the procedures, and to confirm how many patients have more stroke-like symptoms or experience worsening of their thinking skills. This information is needed to be sure that a very large clinical trial to find out if these drugs can prevent worsening of small vessel disease will be possible.

### Who can participate?

Adults aged 30 and older who have had a small vessel stroke.

### What does the study involve?

Participants are randomly allocated to one of four groups. Those in the first group receive cilostazol by mouth twice a day. Those in the second group receive the isosorbide mononitrate by mouth 20 mg twice a day or 50 mg once a day if the extended release formulation used. Those in the third group receive both medications in the same doses and ways above. Those in the last group do not receive any treatment. The treatment lasts one year. Participants are followed up around one to two weeks and three to four weeks by phone as well as six and 12 months by a phone or face to face meeting to assess the tolerability and safety of the medication. The last follow up visit includes a brain scan.

What are the possible benefits and risks of participating?

There are no direct benefits with participation, although some patients find the regular checkups reassuring and the MRI Brain scan may give more details to your doctors about their stroke. There are no foreseeable risks however there is a chance that you may experience side effects from the Trial drugs. Both drugs have been used for many years to treat other conditions so the side effects are well known. If any of these occur, they are usually noticed when first starting the tablets.

Where is the study run from?

- 1. Royal Infirmary of Edinburgh (UK)
- 2. Nottingham City Hospital (UK)
- 3. NHS Fife, Victoria Hospital (UK)
- 4. Queen Elizabeth University Hospital Glasgow (UK)
- 5. Bradford Royal Infirmary (UK)
- 6. Aberdeen Royal Infirmary (UK)
- 7. Leeds General Infirmary (UK)
- 8. Royal Derby Hospital Centre (UK)
- 9. Raigmore Hospital Inverness (UK)
- 10. St George's Hospital London (UK)
- 11. King's College Hospital London (UK)
- 12. Broomfield Hospital Essex (UK)
- 13. University Hospital of North Tees (UK)
- 14. Royal Hallamshire Hospital (UK)
- 15. Sandwell General Hospital (UK)
- 16. Royal Hampshire County Hospital (UK)
- 17. University College London (UK)
- 18. Northwick Park Hospital (UK)
- 19. Luton and Dunstable NHSFT University Hospital (UK)
- 20. Doncaster Royal Infirmary (UK)
- 21. New Cross Hospital Wolverhampton (UK)
- 22. Calderdale Royal Hospital (UK)
- 23. Musgrove Park Hospital (UK)
- 24. Southampton General Hospital (UK)
- 25. Homerton University Hospital (UK)
- 26. Royal Devon and Exeter Hospital (UK)

When is the study starting and how long is it expected to run for? May 2017 to May 2022 (Updated 08/08/2022, previously August 2022. Updated 18/11/2020, previously: December 2022)

Who is funding the study?
British Heart Foundation (BHF) (UK)

Who is the main contact? Professor Joanna Wardlaw Joanna.Wardlaw@ed.ac.uk

Previous plain English summary as of 11/09/2019:

Background and study aims

About 35,000 people each year in the UK have a type of stroke, called 'lacunar' or 'small vessel' stroke, which is different to other common types of stroke and for which there is no proven

treatment. Small vessel stroke may be caused by damage to the lining of the tiny blood vessels deep inside the brain that stops them functioning normally. This not only causes stroke but, perhaps more importantly, causes problems with thinking and walking, possibly causing up to 45% of all dementias either on its own, or mixed with Alzheimer's disease (about 350,000 patients in the UK). Some drugs that are commonly used in other blood vessel diseases may help improve small vessel function and prevent worsening of brain damage. One drug (cilostazol) has been tested in patients with stroke in the Asia Pacific countries but not on dementia; the other drug (isosorbide mononitrate) is widely used in the UK for heart disease but not stroke. The aim of this study is to test if the study methods are practical so that patients and trial centres can follow the procedures, and to confirm how many patients have more stroke-like symptoms or experience worsening of their thinking skills. This information is needed to be sure that a very large clinical trial to find out if these drugs can prevent worsening of small vessel disease will be possible.

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- 2. Nottingham City Hospital (UK)

When is the study starting and how long is it expected to run for? May 2017 to November 2020

Who is funding the study? British Heart Foundation (BHF) (UK)

Who is the main contact?

1. Dr Anna Heye
anna.heye@ed.ac.uk
2. Professor Joanna Wardlaw
Joanna.Wardlaw@ed.ac.uk

Previous plain English summary:

Background and study aims

About 35,000 people each year in the UK have a type of stroke, called 'lacunar' or 'small vessel' stroke, which is different to other common types of stroke and for which there is no proven treatment. Small vessel stroke may be caused by damage to the lining of the tiny blood vessels deep inside the brain that stops them functioning normally. This not only causes stroke but, perhaps more importantly, causes problems with thinking and walking, possibly causing up to 45% of all dementias either on its own, or mixed with Alzheimer's disease (about 350,000 patients in the UK). Some drugs that are commonly used in other blood vessel diseases may help improve small vessel function and prevent worsening of brain damage. One drug (cilostazol) has been tested in patients with stroke in the Asia Pacific countries but not on dementia; the other drug (isosorbide mononitrate) is widely used in the UK for heart disease but not stroke. The aim of this study is to test if the study methods are practical so that patients and trial centres can follow the procedures, and to confirm how many patients have more stroke-like symptoms or experience worsening of their thinking skills. This information is needed to be sure that a very large clinical trial to find out if these drugs can prevent worsening of small vessel disease will be possible.

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When is the study starting and how long is it expected to run for? May 2017 to November 2020

Who is funding the study?
British Heart Foundation (BHF) (UK)

Who is the main contact?

1. Dr Julia Boyd
julia.boyd@ed.ac.uk

2. Professor Joanna Wardlaw Joanna.Wardlaw@ed.ac.uk

### Study website

https://stroke.nottingham.ac.uk/laci-2/

# Contact information

### Type(s)

Scientific

#### Contact name

Prof Joanna Wardlaw

### **ORCID ID**

http://orcid.org/0000-0002-9812-6642

### Contact details

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University of Edinburgh
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Edinburgh
United Kingdom
EH16 4SB
+44 (0)131 465 9599
Joanna.Wardlaw@ed.ac.uk

# Type(s)

**Public** 

#### Contact name

Prof Joanna Wardlaw

### Contact details

Neuroimaging Sciences
University of Edinburgh
Centre for Clinical Brain Sciences (CCBS)
Chancellor's Building
49 Little France Crescent
Edinburgh
United Kingdom
EH16 4SB
+44 (0)131 465 9599
Joanna.Wardlaw@ed.ac.uk

# Additional identifiers

# **EudraCT/CTIS** number

### **IRAS** number

### ClinicalTrials.gov number

NCT03451591

### Secondary identifying numbers

CPMS 36168

# Study information

#### Scientific Title

LACunar Intervention (LACI-2) Trial-2: Assessment of safety and efficacy of cilostazol and isosorbide mononitrate to prevent recurrent lacunar stroke and progression of cerebral small vessel disease

### Acronym

LACI-2

### Study objectives

The trial hypothesis is to test whether a much larger scale study testing the effects of Cilostazol and ISMN on preventing brain damage from small vessel disease will be feasible. We will assess how easy is it to identify suitable patients, how many of them are willing to take part in the study and how many stay on the study for the full 12 months. Feedback from participants on study procedures/burden will also inform any future studies. We will also collect information on how many patients have another stroke, experience difficulties in independent daily living or in thinking skills, and on drug safety such as bleeding.

# Ethics approval required

Old ethics approval format

# Ethics approval(s)

East Midlands - Nottingham 2 REC, 10/05/2017, ref: 17/EM/0077

# Study design

Randomized; Interventional; Design type: Treatment, Drug

# Primary study design

Interventional

# Secondary study design

Randomised controlled trial

# Study setting(s)

Hospital

# Study type(s)

**Treatment** 

### Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

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

Prevention of stroke

#### **Interventions**

Randomisation involves minimisation on a number of key prognostic factors. An electronic randomisation system is used to allocate participants to one of four groups as detailed below. All patients receive best medical therapy for stroke prevention in addition to their randomly allocated trial treatment. Trial treatment period is 54 weeks.

- 1. Cilostazol: oral, 100 mg twice a day
- 2. Isosorbide mononitrate (ISMN): oral, 20 mg twice a day or 50 mg once a day if extended release formulation used
- 3. Cilostazol + ISMN same doses as above
- 4. No trial treatment

There are 4 follow-up time points:

- 1. One-two week follow-up by phone
- 2. Three-four week follow-up by phone
- 3. Six month follow-up by phone or face to face
- 4. 12 month follow-up by phone or face to face

At the end of the 12 months they will stop their allocated treatment, have their final visit which includes a brain scan.

# Intervention Type

Drug

### Phase

Phase II

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

Cilostazol. Isosorbide mononitrate

### Primary outcome measure

Feasibility of a future Phase III trial is the primary outcome and is measured at 36 months. This will be attained if the feasibility target sample size of 400 patients are recruited in 24 months in the UK and >95% retained in follow-up at one year.

### Secondary outcome measures

- 1. Assessment of drug tolerability are measured using questionnaires and reviewing patient notes at one-two weeks, three-four weeks, six months and 12 months
- 2. Safety is measured using questionnaires and reviewing patient notes at one-two weeks, three-four weeks, six months and 12 months
- 3. Event is measured using questionnaires and reviewing patient notes at one-two weeks, three-four weeks, six months and 12 months
- 4. Recruitment rates are measured using questionnaires and reviewing patient notes at one-two

weeks, three-four weeks, six months and 12 months. Questionnaires include a study specific structured questionnaire to record symptoms, medication history and IMP adherence and a vascular event questionnaire.

Overall study start date 01/11/2017

Completion date 31/05/2022

# Eligibility

### Key inclusion criteria

- 1. Clinical lacunar stroke syndrome.
- 2. Brain scanning\* with MR including diffusion imaging wherever possible, and obtained soon after the presentation with stroke, shows either:
- 2.1. A recent, relevant (in time and location) acute lacunar infarct on diffusion MR imaging1, 2.2. Or, if no visible acute lacunar infarct on diffusion MR imaging2 then there is no competing pathology as a cause for stroke (e.g. no acute cortical infarct, no acute intra-cerebral haemorrhage, no stroke mimic such as tumour, subdural haematoma);
- 2.3. If only a CT brain scan is available as in section 3 above, then there is a small relevant (in age and location) subcortical infarct, or if no infarct then there is no competing pathology as a cause for stroke (e.g. no acute cortical infarct, no acute intra-cerebral haemorrhage, no stroke mimic such as tumour, subdural haematoma). Note that if there is no acute lacunar infarct on MR diffusion imaging but there is a recent-appearing lacunar infarct on FLAIR, T2, or T1 (i.e. no cavitation or ex-vacuo effect; may be slightly swollen, ill-defined edges; or scan in the few weeks before the stroke does not show a lesion but there is an acute lacunar infarct on MR T2, FLAIR, T1 scanning after the stroke in an appropriate area of the brain for symptoms), then the T2, FLAIR, T1 lesion may be counted as the acute lacunar infarct in the absence of a diffusion lesion. Similarly, on CT2 a recent relevant small subcortical infarct would not show cavitation or shrinkage/ex vacuo effect. Note that about a third of patients with a clinically definite lacunar syndrome do not have a corresponding recent infarct visible on MRI but should still be classed as 'lacunar stroke' if no other explanation can be found for the symptoms. The presence of a recent cortical infarct on FLAIR, T2, T1, the recent timing being indicated by the characteristics above, would count as a competing pathology. Note that the complete absence of any abnormality on MR or CT brain imaging (no acute subcortical infarct or pre-existing SVD such as white matter hyperintensities, lacunes, etc.) while occasionally seen in lacunar stroke is unusual and should question the diagnosis of lacunar ischaemic stroke.
- 3. Age >30 years
- 4. Independent in activities of daily living (modified Rankin  $\leq$ 2)
- 5. Capacity to give consent themselves

# Participant type(s)

Patient

# Age group

Adult

# Lower age limit

30 Years

### Sex

Both

### Target number of participants

Planned Sample Size: 400; UK Sample Size: 400

### Total final enrolment

363

### Key exclusion criteria

- 1. Other significant active neurological illness present since suffering stroke (e.g. recurrent seizures, multiple sclerosis, brain tumour). Well-controlled epilepsy present prior to the stroke, a single seizure at onset of the stroke or provoked seizure is not an exclusion.
- 2. Requiring assistance with activities of daily living (Modified Rankin ≥3)
- 3. Has been diagnosed as having dementia on formal clinical assessment
- 4. Active cardiac disease (atrial fibrillation, myocardial infarction in past 6 months, active angina, symptomatic cardiac failure)
- 5. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100mmHg
- 6. Definite indication for (i.e. already prescribed) either trial medication, or definite contraindication to a trial drug as per SmPCSPCs lactose intolerance is a contraindication to ISMN preparations which contain lactose monohydrate (indication for or contraindication to one of the trial drugs still allows randomisation to the other trial drug)
- 7. Unable to swallow tablets
- 8. 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)
- 9. Unlikely to comply with trial medication based on knowledge of past history, lifestyle 10. 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.
- 11. Other concurrent life threatening illness
- 12. Unlikely to be available for follow-up (eg moving outside or visitor to the area)
- 13. History of drug overdose or attempted suicide or significant active mental illness
- 14. Pregnant or breastfeeding women, women of childbearing age not taking contraception. Acceptable contraception in women of childbearing age is a "highly effective" contraceptive measure as defined by the Clinical Trials Facilitation Group (http://www.hma.eu/fileadmin/dateien/Human Medicines/01-About HMA/Working Groups/CTFG
- /2014\_09\_HMA\_CTFG\_Contraception.pdf) and includes combined (oestrogen and progesterone containing) or progesterone-only contraception associated with inhibition of ovulation, or intrauterine device or bilateral tubal occlusion. Contraception must be continued for up to 30 days after the end of the IMP dosing schedule.
- 15. Prohibited medications to either trial drug (see sections 4.5 of the appended SmPCSPCs and protocol section 6.6.3, plus no anticoagulant drugs); (prohibited medications to one of the trial drugs still allows randomisation to the other trial drug)
- 16. Renal impairment (creatinine clearance <25 ml/min)
- 17. Hepatic impairment
- 18. Current enrolment in another Clinical Trial of Investigational Medicinal Product (CTIMP); still in extended follow-up beyond the CTIMP primary outcome and no longer taking that trial's IMP

is not an exclusion to enrolment in LACI-2
19. Unable to tolerate MRI or contraindication to MRI (Claustrophobia, Pacemaker)

# Date of first enrolment

08/01/2018

# Date of final enrolment

31/05/2021

# Locations

### Countries of recruitment

England

Scotland

United Kingdom

# Study participating centre Royal Infirmary of Edinburgh (Lead centre)

Royal Infirmary of Edinburgh 51 Little France Drive Edinburgh United Kingdom EH16 4SA

# Study participating centre Nottingham City Hospital

Hucknall Road Nottingham United Kingdom NG5 1PB

# Study participating centre NHS Fife, Victoria Hospital

Hayfield Road Kirkcaldy United Kingdom KY2 5AH

Study participating centre Queen Elizabeth University Hospital Glasgow 1345 Govan Rd Glasgow United Kingdom G51 4TF

# Study participating centre Bradford Royal Infirmary

Duckworth Lane Bradford United Kingdom BD9 6RJ

# Study participating centre Aberdeen Royal Infirmary

Foresterhill Aberdeen United Kingdom AB25 2ZN

# Study participating centre Leeds General Infirmary

Martin Wing Great George Street Leeds United Kingdom LS1 3EX

# Study participating centre Royal Derby Hospital Centre

Uttoxeter Road Derby United Kingdom DE22 3DT

# Study participating centre Raigmore Hospital Inverness

Old Perth Road Inverness United Kingdom IV2 3UJ

# Study participating centre St George's Hospital

Blackshaw Road London United Kingdom SW17 0QT

# Study participating centre King's College Hospital London

Denmark Hill London United Kingdom SE5 9RS

# Study participating centre Broomfield Hospital Essex

Court Road Chelmsford United Kingdom CM1 7ET

# Study participating centre University Hospital of North Tees

Stroke Unit Ward 41 Stockton on Tees United Kingdom TS19 8PE

# Study participating centre Royal Hallamshire Hospital

Glossop Road Sheffield United Kingdom S10 2JF

# Study participating centre Sandwell General Hospital

Lyndon West Bromwich United Kingdom B71 4HJ

# Study participating centre Royal Hampshire County Hospital

Romsey Road Winchester United Kingdom SO22 5DG

# Study participating centre University College London

London United Kingdom WC1N 3BG

# Study participating centre Northwick Park Hospital

Watford Road Harrow United Kingdom HA1 3UJ

# Study participating centre Luton and Dunstable NHSFT University Hospital

Lewsey Road Luton United Kingdom LU4 0DZ

# Study participating centre Doncaster Royal Infirmary

Doncaster United Kingdom DN2 5LT

# Study participating centre New Cross Hospital Wolverhampton Wolverhampton Road

Wolverhampton United Kingdom WV10 0QP

# Study participating centre Calderdale Royal Hospital

Salterhebble Halifax United Kingdom HX3 0PW

# Study participating centre Musgrove Park Hospital

Taunton United Kingdom TA1 5DA

# Study participating centre Southampton General Hospital

Tremona Road Southampton United Kingdom SO16 6YD

# Study participating centre Homerton University Hospital

Homerton Row London United Kingdom E9 6SR

# Study participating centre Royal Devon and Exeter Hospital

Barrack Road Exeter United Kingdom EX2 5DW

# Sponsor information

### Organisation

University of Edinburgh and NHS Lothian - co-sponsors (UK)

### Sponsor details

ACCORD Office
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ

### Sponsor type

University/education

#### **ROR**

https://ror.org/03q82t418

# Funder(s)

### Funder type

Government

### **Funder Name**

British Heart Foundation (BHF)

# **Results and Publications**

### Publication and dissemination plan

Current publication and dissemination plan as of 14/02/2020:

We are going to publish the study protocol in a peer-reviewed journal before the end of recruitment.

A Statistical Analysis Plan will be published prior to database lock and will describe analysis procedures and procedures for missing, unused or spurious data, and definitions of populations analyzed.

On completion of the study, a clinical study report will be prepared for publication in a peer-reviewed journal in accordance with ICH guidelines. A report will also be submitted to the funder (British Heart Foundation). Papers describing secondary analysis will also be published.

The clinical study report will be used for publication and presentation at scientific meetings on stroke and dementia such as UK Stroke Forum, European Stroke Organisation Conference,

International Stroke Conference, the World Stroke Congress, and conferences on Alzheimer's disease and dementia. Investigators have the right to publish orally or in writing the results of the study. Reporting will be in compliance with CONSORT.

Summaries of results will also be made available to all Investigators for dissemination within their clinics (where appropriate and according to their discretion).

A newsletter will be sent to the participants informing them of the results and of other information relevant to small vessel disease and general information about maintaining a healthy lifestyle.

### Intention to publish date

31/08/2023

# Individual participant data (IPD) sharing plan

Current IPD sharing plan as of 29/06/2023:

The datasets generated during and/or analyzed during the current study are available upon request from Professor Joanna Wardlaw (Joanna.Wardlaw@ed.ac.uk); these data are available in a non-publically available repository.

### Previous IPD sharing plan:

The datasets generated during and/or analyzed during the current study are/will be available upon request from Ms Kat Oatey (laci-2@ed.ac.uk) or Professor Joanna Wardlaw (Joanna. Wardlaw@ed.ac.uk).

### Previous IPD sharing plan:

On completion of the study a clinical study report will be prepared for publication in a peer reviewed journal in accordance with ICH guidelines. A report will also be submitted to the funder (British Heart Foundation). Papers describing secondary analysis will also be published. The clinical study report will be used for publication and presentation at scientific meetings on stroke and dementia such as UK Stroke Forum, European Stroke Organisation Conference, International Stroke Conference, the World Stroke Congress, and conferences on Alzheimer's disease and dementia. Investigators have the right to publish orally or in writing the results of the study. Reporting will be in compliance with CONSORT.

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# IPD sharing plan summary

Stored in non-publicly available repository, Available on request

### **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient- facing?
	protocol		20/10		

<u>Protocol article</u>		01/09/2020	/2020	Yes	No
Statistical Analysis Plan	baseline data and statistical analysis plan	02/09/2022	12/10 /2022	Yes	No
Results article	results	24/05/2023	16/06 /2023	Yes	No
HRA research summary			28/06 /2023	No	No
Abstract results		22/05/2019	05/11 /2024	No	No
Abstract results		24/05/2023	05/11 /2024	No	No
Abstract results		01/09/2021	05/11 /2024	No	No
Abstract results		26/05/2023	05/11 /2024	No	No