



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Cilostazol and isosorbide mononitrate for the prevention of progression of : baseline data and statistical analysis plan for the Lacunar Intervention Trial-2 (LACI-2) (ISRCTN14911850)

Citation for published version:

Bath, PM, Mhlanga, I, Woodhouse, LJ, Doubal, F, Oatey, K, Montgomery, AA & Wardlaw, JM 2022, 'Cilostazol and isosorbide mononitrate for the prevention of progression of : baseline data and statistical analysis plan for the Lacunar Intervention Trial-2 (LACI-2) (ISRCTN14911850)', *Stroke and Vascular Neurology*, pp. svn-2022-001816. <https://doi.org/10.1136/svn-2022-001816>

Digital Object Identifier (DOI):

[10.1136/svn-2022-001816](https://doi.org/10.1136/svn-2022-001816)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Stroke and Vascular Neurology

General rights





Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Cilostazol and isosorbide mononitrate for the prevention of progression of : baseline data and statistical analysis plan for the Lacunar Intervention Trial-2 (LACI-2) (ISRCTN14911850)

Philip M Bath ¹, Iris Mhlanga,¹ Lisa J Woodhouse ¹, Fergus Doubal ², Katherine Oatey,³ Alan A Montgomery,⁴ Joanna M Wardlaw ²

To cite: Bath PM, Mhlanga I, Woodhouse LJ, *et al.* Cilostazol and isosorbide mononitrate for the prevention of progression of : baseline data and statistical analysis plan for the Lacunar Intervention Trial-2 (LACI-2) (ISRCTN14911850). *Stroke & Vascular Neurology* 2022;**0**. doi:10.1136/svn-2022-001816

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/svn-2022-001816>).

Received 29 June 2022
Accepted 16 August 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Stroke Trials Unit, University of Nottingham, Nottingham, UK

²Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

³Edinburgh Clinical Trials Unit, University of Edinburgh, Edinburgh, UK

⁴Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK

Correspondence to

Professor Philip M Bath;
philip.bath@nottingham.ac.uk

ABSTRACT

Background Cerebral small vessel disease (SVD) causes lacunar strokes (25% of all ischaemic strokes), physical frailty and cognitive impairment and vascular and mixed dementia. There is no specific treatment to prevent progression of SVD.

Methods The LACunar Intervention Trial-2 is an investigator-initiated prospective randomised open-label blinded-endpoint phase II feasibility study assessing cilostazol and isosorbide mononitrate for preventing SVD progression. We aimed to recruit 400 patients with clinically evident lacunar ischaemic stroke and randomised to cilostazol, isosorbide mononitrate, both or neither, in addition to guideline secondary ischaemic stroke prevention, in a partial factorial design. The primary outcome is feasibility of recruitment and adherence to medication; key secondary outcomes include: drug tolerability; recurrent vascular events, cognition and function at 1 year after randomisation; and safety (bleeding, falls, death). Data are number (%) and median (IQR).

Results The trial commenced on 5 February 2018 and ceased recruitment on 31 May 2021 with 363 patients randomised, with the following baseline characteristics: average age 64 (56.0, 72.0) years, female 112 (30.9%), stroke onset to randomisation 79.0 (27.0, 244.0) days, hypertension 267 (73.6%), median blood pressures 143.0 (130.0, 157.0)/83.0 (75.0, 90.0) mm Hg, current smokers 67 (18.5%), educationally achieved end of school examinations (A-level) or higher 118 (32.5%), modified Rankin scale 1.0 (0.0, 1.0), National Institutes Health stroke scale 1.0 (1.4), Montreal Cognitive Assessment 26.0 (23.0, 28.0) and total SVD score on brain imaging 1.0 (0.0, 2.0). This publication summarises the baseline data and presents the statistical analysis plan.

Summary The trial is currently in follow-up which will complete on 31 May 2022 with results expected in October 2022.

Trial registration number ISRCTN14911850.

INTRODUCTION

Cerebral small vessel disease (SVD) is a major cause of stroke (lacunar ischaemic stroke), intracerebral haemorrhage and vascular and mixed dementias.¹ It is most commonly

due to an intrinsic disorder of the brain's small perforating arterioles with endothelial dysfunction manifesting as impaired vasoreactivity, vascular stiffness, blood–brain barrier leakage and perivascular inflammation.¹ Currently, there is no specific secondary prevention for lacunar ischaemic stroke or SVD-associated cognitive decline.² Combined aspirin and clopidogrel increased bleeding³ and intensive antihypertensive therapy did not reduce recurrence or prevent cognitive decline⁴ in lacunar ischaemic stroke.

However, there are other potential interventions that might prevent SVD or reduce its development and progression, including: drugs that modulate the blood–brain barrier or lower blood lipids, immunosuppressive agents, neurotrophins, peroxisome proliferator-activated receptor-gamma agonists, rho-kinase antagonists, vitamins, anti-inflammatory agents and xanthine oxidase inhibitors.^{2,5} Additionally, drugs that modulate the nitric oxide (NO)-cyclic guanylate cyclase-phosphodiesterase-5 and prostacyclin (PGI₂)-cyclic adenylylase-cyclase-phosphodiesterase-3 systems are attractive since they mimic key endogenous vaso-regulators.² Both NO and PGI₂ have vasodilator, antiplatelet, antileucocyte,⁶ antismooth muscle and proendothelial effects. NO may be administered orally as substrate (L-arginine or inorganic nitrate), organic nitrates (such as isosorbide mononitrate, ISMN) or drugs that inhibit PDE5 (such as dipyridamole⁷ or sildenafil) to increase and preserve levels of the NO second messenger, cyclic guanylate monophosphate. Although PGI₂ has to be administered intravenously, PDE3 may be inhibited with cilostazol,⁸ which preserves levels of the PGI₂ second messenger, cyclic adenylylase monophosphate; cilostazol has showed promise in secondary prevention

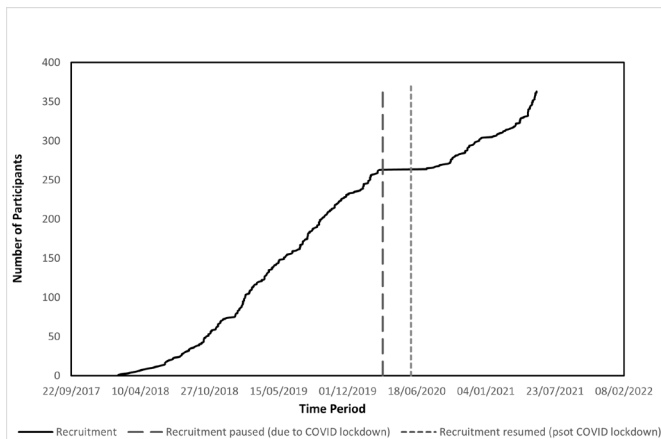


Figure 1 Recruitment by time.

trials in ischaemic stroke, which included large proportions of patients with lacunar stroke subtype⁸; and is widely used in East Asia. In addition, in experimental models, cilostazol reversed impaired oligodendrocyte precursor cell maturation which occurs when endothelial cells are dysfunctional thus potentially reducing myelin damage and facilitating its repair,⁹ and increased the astrocyte-to-neuron lactate shuttle thus increasing energy supply and prolonging neuronal survival.¹⁰ Both actions are potentially relevant to reducing brain damage in SVD.

SVD can present clinically as lacunar ischaemic stroke, cognitive impairment, mobility and/or mood disorders, or be covert and detected on incidentally on brain imaging.¹

Table 1 Continued

| Variable | N | Participants | cSVD | Score* |
|--|-----|----------------|----------------|--------------------|
| | | All | None/mild | Moderate to severe |
| ACE-inhibitors | | 132 (36.4) | 32 (32.3) | 100 (37.9) |
| Angiotensin-II RA | | 54 (14.9) | 14 (14.1) | 40 (15.2) |
| Renin inhibitor | | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Beta-RA | | 41 (11.3) | 10 (10.1) | 31 (11.7) |
| CCB | | 164 (45.2) | 33 (33.3) | 131 (49.6) |
| Diuretic | | 51 (14.0) | 13 (13.1) | 38 (14.4) |
| Alpha-RA | | 17 (4.7) | 3 (3.0) | 14 (5.3) |
| Centrally active | | 2 (0.6) | 1 (1.0) | 1 (0.4) |
| Antiplatelet | 363 | 352 (97.0) | 97 (98.0) | 255 (96.6) |
| Lipid lowering | 363 | 341 (93.9) | 91 (91.9) | 250 (94.7) |
| Proton pump inhibitor | 363 | 128 (35.3) | 30 (30.3) | 98 (37.1) |
| PDE5 inhibitor | 363 | 7 (1.9) | 3 (3.0) | 4 (1.5) |
| Grapefruit juice more than once a week | 363 | 15 (0.04) | 3 (0.03) | 12 (0.04) |
| Other drugs | 363 | 236 (65.0) | 67 (67.7) | 169 (64.0) |
| Nor of drugs taken/day | 363 | 4.0 (3.0, 4.0) | 3.0 (3.0, 4.0) | 4.0 (3.0, 5.0) |

Data are number (%), median (IQR).
 *According to scan read at site.
 †Minimisation variable.
 ‡School exams at age 16 (O-level/GCSE or equivalent) and 18 (A-level or equivalent).
 CCB, calcium channel blocker; F/T, full time; P/T, part time; RA, receptor antagonist; SVD, small vessel disease; TIA, transient ischaemic attack.

Table 1 Baseline characteristics by small vessel disease score as determined by recruiting site

| Variable | N | Participants | cSVD | Score* |
|-------------------------------------|-----|-------------------|-------------------|--------------------|
| | | All | None/mild | Moderate to severe |
| No of patients, N | | 363 | 99 | 264 |
| Demographics | | | | |
| Age, years† | 363 | 64.0(56.0, 72.0) | 62.0(54.0, 69.0) | 65.0(57.5, 73.0) |
| ≤70 years (%) | 363 | 251 (69.1) | 78 (78.8) | 173 (65.5) |
| Sex, female (%) | 363 | 112 (30.9) | 28 (28.3) | 84 (31.8) |
| modified Rankin Scale (/6) | 363 | 1.0(0.0, 1.0) | 1.0(0.0, 1.0) | 1.0(0.0, 1.0) |
| >1 (%)‡ | 363 | 85 (23.4) | 23 (23.2) | 62 (23.5) |
| Onset to randomisation (days)† | 363 | 79.0(27.0, 244.0) | 73.0(27.0, 244.0) | 84.5(28.5, 246.5) |
| ≤100 (%) | 363 | 206 (56.7) | 64 (64.6) | 142 (53.8) |
| Age completing education (years) | 363 | 16.0(15.0, 18.0) | 16.0(15.0, 17.0) | 16.0(15.0, 18.0) |
| Highest education level (%)‡ test | | | | |
| Primary school | 363 | 2 (0.6) | 0 (0.0) | 2 (0.8) |
| Secondary school | 363 | 129 (35.5) | 36 (36.4) | 93 (35.2) |
| O-level/GCSE or equivalent‡ | 363 | 114 (31.4) | 34 (34.3) | 80 (30.3) |
| A-level or equivalent‡ | 363 | 54 (14.9) | 17 (17.2) | 37 (14.0) |
| College or university undergraduate | 363 | 37 (10.2) | 7 (7.1) | 30 (11.4) |
| College or university postgraduate | 363 | 27 (7.4) | 5 (5.1) | 22 (8.3) |
| Lifestyle | | | | |
| Smoking (%)† | | | | |
| Current | 363 | 67 (18.5) | 17 (17.2) | 50 (18.9) |
| Past | 363 | 154 (42.4) | 36 (36.4) | 118 (44.7) |
| Never | 363 | 142 (39.1) | 46 (46.5) | 96 (36.4) |
| Medical history (%) | | | | |
| Hypertension | 363 | 267 (73.6) | 58 (58.6) | 209 (79.2) |
| Hypertension, drug treated | 363 | 258 (71.1) | 55 (55.6) | 203 (76.9) |
| Hyperlipidaemia | 363 | 281 (77.4) | 75 (75.8) | 206 (78.0) |
| Hyperlipidaemia, drug treated | 363 | 278 (76.6) | 75 (75.8) | 203 (76.9) |
| Diabetes mellitus | 363 | 80 (22.0) | 20 (20.2) | 60 (22.7) |
| Insulin | 363 | 18 (5.0) | 5 (5.1) | 13 (4.9) |
| Oral agents | 363 | 58 (16.0) | 18 (18.2) | 40 (15.2) |
| Lifestyle | 363 | 24 (6.6) | 3 (3.0) | 21 (8.0) |
| Atrial fibrillation | 363 | 5 (1.4) | 1 (1.0) | 4 (1.5) |
| Heart failure | 363 | 4 (1.1) | 0 (0.0) | 4 (1.5) |
| Previous stroke | 363 | 25 (6.9) | 2 (2.0) | 23 (8.7) |
| Prior TIA | 363 | 29 (8.0) | 5 (5.1) | 24 (9.1) |
| Family history, young stroke | 363 | 55 (15.2) | 16 (16.2) | 39 (14.8) |
| Current medications (%) | | | | |
| Anticoagulants | 363 | 5 (1.4) | 1 (1.0) | 4 (1.5) |
| Antibiotics | 363 | 2 (0.6) | 0 (0.0) | 2 (0.8) |
| Antihypertensive | 363 | 277 (76.3) | 67 (67.7) | 210 (79.5) |

Continued

Table 2 Baseline clinical and investigation characteristics by small vessel disease score as determined by recruiting site

| Variable | N | Participants | cSVD | Score* | P value |
|-------------------------------------|-----|----------------------|----------------------|----------------------|---------|
| | | All | None/mild | Moderate to severe | |
| No of patients, N | | 363 | 99 | 264 | |
| Clinical data (%) | | | | | |
| SBP mm Hg† | 363 | 143.0 (130.0, 157.0) | 143.0 (128.0, 160.0) | 143.0 (131.0, 155.5) | 0.94 |
| DBP mm Hg | 363 | 83.0 (75.0, 90.0) | 82.0 (75.0, 90.0) | 83.0 (75.5, 90.0) | 0.89 |
| NIHSS (/42)† | 363 | 0.0 (0.0, 2.0) | 0.0 (0.0, 1.0) | 0.0 (0.0, 2.0) | 0.34 |
| Duration of symptoms (days) | 145 | 2.0 (1.0, 5.0) | 2.0 (1.0, 7.0) | 2.0 (1.0, 5.0) | 0.30 |
| Ongoing symptoms | 363 | 218 (60.1) | 58 (58.6) | 160 (60.6) | 0.73 |
| Weakness, side of weakness | 363 | 288 (79.3) | 80 (80.8) | 208 (78.8) | 0.67 |
| Left (%) | 363 | 148 (40.8) | 37 (37.4) | 111 (42.0) | |
| Right (%) | 363 | 138 (38.0) | 43 (43.4) | 95 (36.0) | |
| Both (%) | 363 | 2 (0.6) | 0 (0.0) | 2 (1.0) | |
| Sensory loss, side of loss | 363 | 148 (40.8) | 43 (43.4) | 105 (39.8) | 0.53 |
| Left (%) | 363 | 74 (20.4) | 19 (19.2) | 55 (20.8) | |
| Right (%) | 363 | 71 (19.6) | 24 (24.2) | 47 (17.8) | |
| Both (%) | 363 | 3 (0.8) | 0 (0.0) | 3 (1.1) | |
| Ataxia | 363 | 84 (23.1) | 17 (17.2) | 67 (25.4) | 0.010 |
| Left (%) | 363 | 41 (11.3) | 5 (5.1) | 36 (13.6) | |
| Right (%) | 363 | 39 (10.7) | 12 (12.1) | 27 (10.2) | |
| Neglect/inattention | 363 | 6 (1.7) | 1 (1.0) | 5 (1.9) | 0.56 |
| Dysphasia | 363 | 19 (5.2) | 6 (6.1) | 13 (4.9) | 0.67 |
| Dysarthria | 363 | 111 (30.6) | 28 (28.3) | 83 (31.4) | 0.56 |
| Visual loss | 363 | 11 (3.0) | 6 (6.1) | 5 (1.9) | 0.039 |
| Cognition | | | | | |
| MOCA total (/30) | 363 | 26.0 (23.0, 28.0) | 26.0 (23.0, 28.0) | 26.0 (24.0, 28.0) | 0.098 |
| ≤24 (%) | 363 | 119 (32.8) | 39 (39.4) | 80 (30.3) | 0.10 |
| Trail making test part B | | | | | |
| Time (seconds) | 359 | 110.0 (75.0, 170.0) | 112.0 (74.0, 168.0) | 108.0 (76.0, 171.0) | 0.73 |
| Points | 359 | 25.0 (23.0, 25.0) | 25.0 (23.0, 25.0) | 25.0 (23.0, 25.0) | 0.39 |
| Investigations (%) | | | | | |
| Type of scan after index stroke (%) | | | | | |
| CT only | 363 | 101 (27.8) | 40 (40.4) | 61 (23.1) | 0.001 |
| MRI only | 363 | 43 (11.8) | 9 (9.1) | 34 (12.9) | 0.32 |
| Both | 363 | 219 (60.3) | 50 (50.5) | 169 (64.0) | 0.019 |
| Stroke-CT scan (days) | 320 | 1.0 (0.0, 1.0) | 0.0 (0.0, 1.0) | 1.0 (0.0, 1.0) | 0.26 |
| Stroke-MRI scan (days) | 262 | 3.0 (1.0, 9.0) | 2.0 (1.0, 5.0) | 3.0 (1.0, 11.0) | 0.13 |
| Acute stroke lesion present* | 363 | 296 (81.5) | 68 (68.7) | 228 (86.4) | <0.001 |
| Lesion side of brain, left (%)* | 363 | 164 (45.2) | 45 (45.5) | 119 (45.1) | 0.95 |
| SVD score 1 (%)* | 363 | 206 (56.7) | 0 (0.0) | 206 (78.0) | – |
| WMH/hypoattenuations, yes (%)* | 363 | 179 (49.3) | 0 (0.0) | 179 (67.8) | – |
| Total SVD score*† | 363 | 1.0 (0.0, 2.0) | 0.0 (0.0, 0.0) | 1.0 (1.0, 2.0) | – |
| SVD moderate/severe (%)* | 363 | 264 (72.7) | 0 (0.0) | 264 (100.0) | – |
| Carotid stenosis (%) | 363 | 315 (86.8) | 90 (90.9) | 225 (85.2) | 0.16 |
| Degree of stenosis left <50% | 363 | 312 (86.0) | 90 (90.9) | 222 (84.1) | |
| Degree of stenosis right <50% | 363 | 309 (85.1) | 90 (90.9) | 219 (83.0) | |
| ECG (%) | | | | | |
| Sinus | 360 | 347 (96.4) | 94 (95.9) | 253 (96.6) | 0.93 |

Continued



Table 2 Continued

| Variable | N | Participants | cSVD | Score* | P value |
|---------------------|-----|-------------------|-------------------|--------------------|---------|
| | | All | None/mild | Moderate to severe | |
| AF | 360 | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Other | 360 | 13 (3.6) | 4 (4.1) | 9 (3.4) | |
| Haemoglobin, g/L | 361 | 14.2 (13.3, 15.2) | 14.3 (13.2, 15.3) | 14.2 (13.3, 15.2) | 0.55 |
| Creatinine (µmol/l) | 363 | 77.0 (66.0, 90.0) | 82.0 (69.0, 91.0) | 76.0 (66.0, 90.0) | 0.21 |
| eGFR (mL/min) | 362 | 75.0 (75.0, 78.0) | 75.0 (75.0, 81.0) | 75.0 (75.0, 75.0) | 0.10 |

Data are number (%), median (IQR).
 *According to scan read at site.
 †Minimisation variable.
 F/T, full time; NIHSS, National Institutes Health stroke scale; P/T, part time; SVD, small vessel disease; WMH, white matter hyperintensity.

These presentations are associated with increased short and long-term risk of recurrent stroke, cognitive decline, dementia and functional impairments.^{11–15} However, although these clinical outcomes are highly relevant to patients and clinical services,^{15 16} the data on their rates long term, individually or in combination, are sparse, precluding reliable sample size estimations for clinical trials in SVD.¹⁷ Furthermore, it was unclear if patients with clinically evident lacunar ischaemic stroke could be identified with key prognostic variables determined accurately in routine clinical practice, or recruited in sufficient numbers rapidly enough, to make a clinical trial in stroke presentations of SVD feasible in a practical time period. This is because lacunar ischaemic stroke may be confused clinically with mild cortical ischaemic stroke,¹⁸ MRI is not always available acutely nor positive for small subcortical stroke,¹⁹ and long-term outcomes vary with severity of SVD lesions on brain imaging,^{13–15} making it necessary to minimise the randomisation on SVD severity.²⁰ Since lacunar ischaemic stroke is currently managed according to guidelines covering the whole of secondary prevention of ischaemic stroke (representing best medical care) and there is no justification currently for withholding secondary prevention, any novel drugs should be tested against a background of guideline secondary ischaemic stroke prevention.

The LACunar Intervention Trial-2 (LACI-1/2) series of trials are assessing the feasibility of recruiting patients with clinically evident lacunar ischaemic stroke and tolerability of treatment with ISMN and cilostazol,^{17 21–24} while also gathering data on outcome event rates, with the aim of testing these agents in a large phase III efficacy trial. In LACI-1, short-term administration of cilostazol and ISMN in addition to best medical care were well tolerated when the dose was escalated, without safety concerns, in patients with clinically evident lacunar ischaemic stroke²³; additionally, these drugs appeared to reduce arterial stiffness without effects on platelet function²² and appeared to improve cerebrovascular function.²⁴

The present trial, LACI-2, is testing the long-term feasibility and tolerability of administering cilostazol and ISMN to patients with clinically evident lacunar ischaemic stroke given on top of guideline secondary ischaemic

stroke prevention while assessing safety and gathering data on clinically relevant outcome event rates.¹⁷ Here, we present the statistical analysis plan (SAP) and baseline data of LACI-2.

METHODS

The LACunar Intervention Trial-2 (LACI-2) is a UK-based investigator-initiated, prospective, randomised, partial factorial, open-label, blinded-endpoint phase II feasibility trial of cilostazol and/or ISMN. Patients with clinically evident lacunar ischaemic stroke, with no limit on the time interval since the stroke, with capacity to consent and who were independent in activities of daily living, were randomised to cilostazol, ISMN, both or neither in a partial factorial design. Patients with contraindications to one of the trial drugs could be randomised to the other drug alone. Randomised treatment was given in all patients in addition to guideline stroke prevention therapies, typically clopidogrel or aspirin, antihypertensive drugs and statins. Patients requiring oral anticoagulation were excluded.

Full details of regulatory approvals, patient assessment, inclusion and exclusion criteria, randomisation, minimisation criteria (age, baseline modified Rankin scale (mRS), National Institutes Health stroke scale (NIHSS), time from stroke to randomisation, highest educational attainment, smoking, systolic BP), dose-escalation scheme, short-term and long-term assessments are given in the protocol paper.¹⁷

The presence of an infarct relevant to the clinical presentation and a simplified estimate of total SVD lesion severity score, adapted for use on CT or MRI and by people not expert in brain imaging of SVD,^{17 21} were determined at the recruiting site. All diagnostic CT or MRI, scans obtained at any stroke recurrence and 1-year follow-up MRI, were collected by the trial office for central adjudication.

The primary outcome is feasibility of recruitment and adherence to medication. Key secondary outcomes include recruitment of hospital sites and participants, drug tolerability, symptoms (such as headache, nausea, palpitations) which might deter drug adherence, safety

(bleeding, falls, death), recurrent vascular events (including stroke and myocardial infarction), cognition and function over 1 year of follow-up. Imaging outcomes (white matter hyperintensity (WMH) severity, new cortical or subcortical infarcts, lacunes, haemorrhage, microbleeds) are assessed with MRI at 1 year. Details of central CT and MRI adjudication are given in the LACI-2 protocol paper.¹⁷

LACI-2 will provide outcome event rates and hence information to estimate sample size, recruitment and trial procedures for a phase III trial based in clinical outcomes. Further information is given in online supplemental file and published protocol.¹⁷

We present here a complete listing of baseline data; data are number (%) and median (IQR), unless otherwise stated.

The full details of the SAP^{25 26} are given in the accompanying online supplemental file, Appendix S1 and is presented prior to locking of the study database so that analyses are not data driven or reported selectively.²⁷ The SAP also lists planned secondary analyses and substudies, and follows the layout suggested in guidelines.^{25 26}

RESULTS

The trial commenced in February 2018; recruitment was suspended due to COVID-19 restrictions on 17 March 2020 by the Sponsor and reopened on 10 June 2020; however, the additional delays in reinstating site approvals meant that there was a total of 4 months without recruitment. Following a 6-month extension, recruitment stopped on 31 May 2021 to allow a year of follow-up prior to close, a total of 40 months (36 months excluding COVID-19 suspension, figure 1).

Of a planned 400 participants, 363 (91%) were recruited from 26 UK hospitals. At baseline, the average age was 64 (range 31–87) years (table 1). There were 112 (31%) female patients, the median NIHSS was 0 (0, 0), the mRS was 2 in 85 (23%) patients, and the time from stroke onset to randomisation was 79.0 (27.0, 244.0) days (table 1). The median age for completing education was 16 years, with 118 (33%) participants having one or more A-level equivalent or above qualifications. Vascular risk factor rates included median blood pressure of 143.0 (130.0, 157.0)/83.0 (75.0, 90.0) mm Hg, current smoking in 67 (19%), drug-treated hypertension in 258 (71%), drug-treated hyperlipidaemia in 278 (77%), diabetes mellitus in 80 (22%), atrial fibrillation in 5 (1%), carotid stenosis of >50% left 3 (0.8%), right 6 (1.7%) and history of previous stroke in 25 (7%) (table 2).

Baseline clinical findings included persistent unilateral weakness in 288 (79%), sensory change in 148 (41%), neglect/inattention in 6 (2%), dysphasia in 19 (5%) and visual disturbance in 11 (3%) (table 2). On cognitive testing, the median Montreal Cognitive Assessment score was 26.0 (23.0, 28.0) with 119 (33%) having a score below 25 signifying cognitive impairment. The median score on

the trail making test, part B, a test of executive function, was 25.0 (23.0, 25.0) points.

A majority of participants, 219 (60%), had both an admission CT scan and MRI brain imaging (320, 88%, had CT and 229, 65%, had MRI) (table 2). Imaging findings as reported by the recruiting site included an acute ischaemic stroke lesion thought to be consistent with the lacunar stroke symptoms in 296 (82%), WMHs present in 179 (49%) and median modified total SVD score of 1.0 (0.0, 2.0).

On central adjudication, a visible index infarct was present in 319 (88%) and averaged 10×8×10 mm in size (table 3). Only one scan was considered to be normal, that is, to have neither an acute infarct responsible for the recent stroke symptoms or any background changes of SVD or atrophy. Microbleeds were present in 20% of patients in mainly lobar (28%), deep (41%) or mixed lobar/deep (31%) locations (table 4). Atrophy was present in 75% of participants. WMHs were present in 95% of participants: 76% had up to Fazekas 2 periventricular and 82% had up to Fazekas 2 deep WMH scores. Sixty-two per cent of participants had one or more old vascular lesions including lacunes present in 96% (table 5).

In univariate analyses and in comparison with participants with lower SVD scores (table 1), those with moderate or severe SVD scores were older and more likely to have had a previous stroke, be taking antihypertensive drugs and have ataxia, and less likely to have visual loss. Additionally, participants with more severe SVD scores were more likely to have had MRI at diagnosis and to have a relevant acute ischaemic stroke lesion present on imaging (table 3). Similarly, in comparison with participants with a low SVD score, those with a moderate/high score had more atrophy, WMHs and their severity (table 4), and the presence of old vascular lesions (table 5).

DISCUSSION

SVD is common worldwide and, so far, whether presenting covertly or with stroke, cognitive or physical impairment, or neuropsychiatric symptoms,²⁸ has no demonstrated interventions that prevent or limit its development and progression.^{2-4 16} The LACI trials are assessing the tolerability and feasibility of recruiting patients, the outcome event rates, and tolerability and safety of treatment with ISMN and cilostazol^{17 21-24} in addition to guideline secondary stroke prevention, with the aim of testing these agents in a large phase III efficacy trial.

The baseline characteristics presented here show that LACI-2 is representative of patients with clinically evident lacunar ischaemic stroke, a marker of SVD. In particular, the average age was younger than for other types of ischaemic stroke at 64 years,²⁹ there was a preponderance of males (69%)³⁰ and most participants had relatively few physical signs or impairments resulting from their stroke.¹⁵ A majority of participants were diagnosed with hypertension and taking antihypertensive medication, and most were taking antiplatelet or lipid lowering drugs

Table 3 Adjudicated baseline imaging characteristics by small vessel disease score as determined by recruiting site

| Variable | N | All | SVD | Score | P value |
|-------------------------------|-----|------------------|------------------|------------------|---------|
| | | | Low | Moderate-severe | |
| Patients randomised | | 363 | 99 | 264 | |
| Scan | | | | | |
| Scan type (%) | | | | | |
| CT | 363 | 320 (88.2) | 90 (90.9) | 230 (87.1) | 0.32 |
| Time to CT (days) | 320 | 1.0 (0.0, 1.0) | 0.0 (0.0, 1.0) | 1.0 (0.0, 1.0) | 0.19 |
| MRI | 362 | 263 (72.5) | 60 (60.6) | 203 (76.9) | 0.0020 |
| Time to MRI (days) | 263 | 3.0 (1.0, 9.0) | 2.0 (1.0, 5.0) | 3.0 (1.0, 11.0) | 0.097 |
| Scan quality (%) | | | | | 0.28 |
| Good | | 237 (65.3) | 66 (66.7) | 171 (64.8) | |
| Moderate | | 118 (32.5) | 29 (29.3) | 89 (33.7) | |
| Poor | | 8 (2.2) | 4 (4.0) | 4 (1.5) | |
| Index lesion (%) | | | | | |
| Normal scan | | 1 (0.3) | 1 (1.0) | 0 (0.0) | 1.00 |
| Lesion present (type) | | | | | 0.0006 |
| Primary infarct | | 319 (87.9) | 77 (77.8) | 242 (91.7) | |
| Primary haemorrhage | | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Mimic | | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| No acute lesion visible | | 43 (11.8) | 21 (21.2) | 22 (8.3) | |
| Infarct side of brain | 320 | | | | 0.22 |
| Right | | 142 (44.4) | 29 (37.7) | 113 (46.5) | |
| Left | | 175 (54.7) | 48 (62.3) | 127 (52.3) | |
| Both | | 3 (0.9) | 0 (0.0) | 3 (1.2) | |
| Location (%) | 320 | | | | |
| Small subcortical infarct | | 311 (97.2) | 72 (93.5) | 239 (98.4) | 0.33 |
| Internal capsule | | 110 (34.4) | 21 (27.3) | 89 (36.6) | |
| External capsule | | 4 (1.3) | 1 (1.3) | 3 (1.2) | |
| Lentiform nucleus | | 31 (9.7) | 7 (9.1) | 24 (9.9) | |
| Internal border zone | | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Centrum semiovale | | 83 (25.9) | 23 (29.9) | 60 (24.7) | |
| Thalamus | | 64 (20.0) | 17 (22.1) | 47 (19.3) | |
| Cerebellum | | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Brainstem lesion (pons) | | 18 (5.6) | 3 (3.9) | 15 (6.2) | |
| Medulla | | 1 (0.3) | 0 (0.0) | 1 (0.4) | |
| Non-small subcortical infarct | | | | | |
| MCA territory | 320 | 9 (2.8) | 4 (5.2) | 5 (2.1) | 0.23 |
| PCA territory | 320 | 2 (0.6) | 1 (1.3) | 1 (0.4) | 0.42 |
| Infarct size (mm) | 320 | | | | |
| A/P | | 10.0 (8.0, 12.0) | 10.0 (8.0, 12.0) | 10.0 (8.0, 12.0) | 0.97 |
| R/L | | 9.0 (6.0, 11.0) | 9.0 (6.0, 10.0) | 9.0 (6.0, 11.0) | 0.91 |
| Cranio-caudal | | 10.0 (8.0, 15.0) | 10.0 (8.0, 12.0) | 10.0 (8.0, 15.0) | 0.15 |

Data are number (%), median (IQR) or mean (SD). The number of participants with data is 363 unless stated.

Index lesion=main cause of stroke symptoms.

Index small subcortical infarct=acute lacunar.

Non-small subcortical infarct=large artery cortical or large subcortical or posterior circulation.

SVD, small vessel disease.

Table 4 Adjudicated baseline imaging characteristics (microhaemorrhages, atrophy, white matter hyperintensities and perivascular spaces) by small vessel disease score as determined by recruiting site

| Variable | N | SVD | | Score | | P value |
|--|-----|------------|-----------|-----------------|--|---------|
| | | All | Low | Moderate-severe | | |
| Patients randomised | 363 | 99 | 264 | | | |
| Microhaemorrhages | 196 | 39 (19.9) | 9 (20.9) | 30 (19.6) | | 0.85 |
| No microhaemorrhages (%) | 39 | | | | | 0.18 |
| 1 | | 9 (23.1) | 5 (55.6) | 4 (13.3) | | |
| 2 | | 7 (17.9) | 3 (33.3) | 4 (13.3) | | |
| 3 | | 5 (12.8) | 0 (0.0) | 5 (16.7) | | |
| 4 | | 2 (5.1) | 0 (0.0) | 2 (6.7) | | |
| ≥5 | | 15 (38.5) | 1 (11.1) | 14 (46.7) | | |
| Type of microhaemorrhages (%) | 39 | | | | | 0.61 |
| Lobar | | 11 (28.2) | 2 (22.2) | 9 (30.0) | | |
| Deep | | 16 (41.0) | 5 (55.6) | 11 (36.7) | | |
| Both | | 12 (30.8) | 2 (22.2) | 10 (33.3) | | |
| Superficial siderosis present | 41 | 2 (4.9) | 0 (0.0) | 2 (6.3) | | 1.00 |
| Siderosis focal | | 2 (100.0) | 0 (0.0) | 2 (100.0) | | 1.00 |
| Siderosis disseminated | | 0 (0.0) | 0 (0.0) | 0 (0.0) | | – |
| Siderosis location | | | | | | 1.00 |
| Left | | 1 (50.0) | 0 (0.0) | 1 (50.0) | | |
| Right | | 0 (0.0) | 0 (0.0) | 0 (0.0) | | |
| Both | | 1 (50.0) | 0 (0.0) | 1 (50.0) | | |
| Atrophy (%) | | | | | | |
| Brain volume reduction | 362 | 272 (75.1) | 63 (64.3) | 209 (79.2) | | 0.0036 |
| Central brain tissue volume | 272 | | | | | 0.42 |
| Moderate | | 199 (73.2) | 50 (79.4) | 149 (71.3) | | |
| Severe | | 64 (23.5) | 11 (17.5) | 53 (25.4) | | |
| Cortical brain tissue volume | 272 | | | | | 0.12 |
| Moderate | | 203 (74.6) | 43 (68.3) | 160 (76.6) | | |
| Severe | | 5 (1.8) | 0 (0.0) | 5 (2.4) | | |
| WMH (%) | | | | | | |
| WMH present | 362 | 342 (94.5) | 87 (88.8) | 255 (96.6) | | 0.0038 |
| Anterior white matter lucency | 342 | | | | | |
| Adjoining ventricles | | 116 (33.9) | 32 (36.8) | 84 (32.9) | | 0.51 |
| Covering ventricle to cortex | | 56 (16.4) | 6 (6.9) | 50 (19.6) | | 0.0057 |
| Posterior white matter lucency | 342 | | | | | |
| Adjoining ventricles | | 114 (33.3) | 27 (31.0) | 87 (34.1) | | 0.60 |
| Covering ventricle to cortex | | 55 (16.1) | 10 (11.5) | 45 (17.6) | | 0.18 |
| Anterior and/or Posterior white matter lucency | 342 | | | | | |
| Adjoining ventricles | | 136 (39.8) | 36 (41.4) | 100 (39.2) | | 0.72 |

Continued

Table 4 Continued

| Variable | N | SVD | | Score | | P value |
|---|-----|-------------|------------|-----------------|--|---------|
| | | All | Low | Moderate-severe | | |
| Covering ventricle to cortex | | 68 (19.9) | 11 (12.6) | 57 (22.4) | | 0.050 |
| Periventricular WMH Fazekas score | 342 | | | | | <0.0001 |
| 1 | | 131 (38.3) | 48 (55.2) | 83 (32.5) | | |
| 2 | | 129 (37.7) | 32 (36.8) | 97 (38.0) | | |
| 3 | | 80 (23.4) | 7 (8.0) | 73 (28.6) | | |
| Deep WMH Fazekas score | 342 | | | | | 0.0002 |
| 1 | | 178 (52.0) | 59 (67.8) | 119 (46.7) | | |
| 2 | | 102 (29.8) | 14 (16.1) | 88 (34.5) | | |
| 3 | | 42 (12.3) | 5 (5.7) | 37 (14.5) | | |
| Periventricular and/or Deep WMH Fazekas score | 342 | | | | | <0.0001 |
| 1 | | 123 (36.0) | 46 (52.9) | 77 (30.2) | | |
| 2 | | 137 (40.1) | 34 (39.1) | 103 (40.4) | | |
| 3 | | 82 (24.0) | 7 (8.0) | 75 (29.4) | | |
| Enlarged PVS (%), MRI only | 194 | | | | | |
| Enlarged PVS | | 194 (100.0) | 43 (100.0) | 151 (100.0) | | 1.00 |
| Basal ganglia score | | | | | | |
| ≤10 | | 62 (32.0) | 23 (53.5) | 39 (25.8) | | 0.0008 |
| 11–20 | | 74 (38.1) | 16 (37.2) | 58 (38.4) | | |
| 20–40 | | 36 (18.6) | 4 (9.3) | 32 (21.2) | | |
| >40 | | 22 (11.3) | 0 (0.0) | 22 (14.6) | | |
| Centrum semiovale score | | | | | | |
| ≤10 | | 30 (15.5) | 10 (23.3) | 20 (13.2) | | 0.30 |
| 11–20 | | 52 (26.8) | 13 (30.2) | 39 (25.8) | | |
| 20–40 | | 82 (42.3) | 15 (34.9) | 67 (44.4) | | |
| >40 | | 30 (15.5) | 5 (11.6) | 25 (16.6) | | |

Data are number (%), median (IQR) or mean (SD). The number of participants with data is 363 unless stated. PVS, perivascular spaces; WMH, white matter hyperintensities.

as guideline secondary prevention of ischaemic stroke. Many were ex-smokers or current smokers. Very few had atrial fibrillation or carotid stenosis (about 1%) reflecting that, while emboli can enter and intracranial large artery atheroma may obstruct perforating cerebral arterioles, these are rare in, and uncommon causes of, lacunar ischaemic stroke.^{29 31}

A minority of participants had clinical cortical features such as dysphasia (19, 5.2%), neglect (6, 2%) or hemianopia (11, 3%), reflecting the overlap in symptoms between cortical and lacunar ischaemic stroke,¹⁸ and potential difficulty of recruiting pure lacunar syndrome populations on the basis of clinical syndrome and CT scanning in busy regional hospital stroke services. Nonetheless, it is reassuring that very few patients were found to have a primary cortical infarct on central expert scan

Table 5 Adjudicated baseline imaging characteristics (old vascular and non-stroke lesions) by small vessel disease score as determined by recruiting site

| Variable | N | All | SVD | | P value |
|---|-----|------------|-----------|-----------------|---------|
| | | | Low | Moderate-severe | |
| Patients randomised | | 363 | 99 | 264 | |
| Old vascular lesions (%) | 362 | 224 (61.9) | 38 (38.8) | 186 (70.5) | <0.0001 |
| Old cortical infarct | 224 | 11 (4.9) | 1 (2.6) | 10 (5.4) | 0.70 |
| Old striatocapsular infarct | 224 | 2 (0.9) | 1 (2.6) | 1 (0.5) | 0.31 |
| Old borderzone infarct | 224 | 2 (0.9) | 1 (2.6) | 1 (0.5) | 0.31 |
| Old lacunar infarct | 224 | 216 (96.4) | 36 (94.7) | 180 (96.8) | 0.54 |
| No of lacunes (%) | 224 | | | | 0.11 |
| 1 | | 40 (17.9) | 10 (26.3) | 30 (16.1) | |
| 2 | | 46 (20.5) | 8 (21.1) | 38 (20.4) | |
| 3 | | 42 (18.8) | 8 (21.1) | 34 (18.3) | |
| 4 | | 26 (11.6) | 6 (15.8) | 20 (10.8) | |
| ≥5 | | 62 (27.7) | 4 (10.5) | 58 (31.2) | |
| Old brainstem/cerebellar non-lacunar infarcts | 224 | 35 (15.6) | 2 (5.3) | 33 (17.7) | 0.083 |
| Probable old haemorrhage | 224 | 4 (1.8) | 0 (0.0) | 4 (2.2) | 1.00 |
| Non-stroke lesions (%) | | | | | |
| Non-stroke lesion present | 362 | 13 (3.6) | 3 (3.1) | 10 (3.8) | 1.00 |
| Classification of non-stroke (%) | 13 | | | | |
| Cerebral tumour | | 2 (15.4) | 0 (0.0) | 2 (20.0) | 1.00 |
| Aneurysm | | 1 (7.7) | 0 (0.0) | 1 (10.0) | 1.00 |
| Vascular malformation | | 1 (7.7) | 1 (33.3) | 0 (0.0) | 1.00 |
| Other non-stroke classification | | 8 (61.5) | 2 (66.7) | 6 (60.0) | 1.00 |

Data are number (%), median (IQR), or mean (SD). The number of participants with data is 363 unless stated.

read (3%), the remaining 97% having either a recent small subcortical (ie, acute lacunar) infarct as the primary cause of symptoms, or no definite visible relevant lacunar infarct but no alternative cause for their symptoms.

On adjudicated brain imaging, most participants (264, 73%) were judged to have a moderate to severe SVD score by the recruiting hospital, consistent with patients with lacunar ischaemic stroke, and demonstrating that a simplified version of the SVD score, suitable for use on CT or MRI, can be applied in busy stroke services.³²

The trial is in follow-up and once this is completed, the database will be cleaned and locked. Therefore there may be minor changes in the baseline data between that provided here and in subsequent publications. Analysis will follow the SAP given here as an online supplemental file. If reasonable drug adherence and safety are confirmed, then a phase III trial will be

designed and submitted for funding using the vascular and cognitive outcome event rates to power the next phase of the trial.

Acknowledgements We thank the patients and their relatives for their time and effort to participate in LACI-2; and the Trial Steering Committee, Sponsor, Data Monitoring Committee, Edinburgh Clinical Trials Unit staff, UK Clinical Research Network, Scottish Stroke Research Network, International Advisory Panel, and all staff at participating sites (listed in the protocol paper (Ref 17)), for their support.

Contributors JMW is the chief investigator, obtained ethics and regulatory approvals; PMB is Director of the Nottingham Stroke Trials Unit. KO is the current trial manager, responsible for daily running of the trial including regulatory compliance; FD is a Principle Investigator; AAM provides statistical expertise; IM and LJW are the trial statisticians; PMB drafted the manuscript; all other authors commented and edited it; all authors approved the final version for submission. JMW is the guarantor for the trial.

Funding The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work is supported by British Heart Foundation (CS/15/5/31475), the Alzheimer's Society (AS-PG-14-033), EU Horizon 2020 SVDs@Target (666881), MRC UK DRI, Fondation Leducc (16/05 CVD), NHS Research Scotland, The Stroke Association and Garfield-Weston Foundation, Chief Scientist Office (UC), and National Institute of Health Research. PMB is Stroke Association Professor of Stroke Medicine and an Emeritus NIHR Senior Investigator.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by East Midlands Nottingham 2 Research Ethics Committee of the Health Research Authority number 17/EM/0077 on 10/05/2017. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Not applicable since main paper/results yet to be analysed and published.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Philip M Bath <http://orcid.org/0000-0003-2734-5132>

Lisa J Woodhouse <http://orcid.org/0000-0002-4472-1999>

Fergus Doubal <http://orcid.org/0000-0002-2769-3148>

Joanna M Wardlaw <http://orcid.org/0000-0002-9812-6642>

REFERENCES

- 1 Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019.
- 2 Bath PM, Wardlaw JM. Pharmacological treatment and prevention of cerebral small vessel disease: a review of potential interventions. *Int J Stroke* 2015;10:469–78.
- 3 , Benavente OR, Hart RG, et al, SPS3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012;367:817–25.
- 4 , Benavente OR, Coffey CS, et al, SPS3 Study Group. Blood-Pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;382:507–15.
- 5 Appleton JP, Scutt P, Sprigg N, et al. Hypercholesterolaemia and vascular dementia. *Clin Sci* 2017;131:1561–78.

- 6 Bath PM, Hassall DG, Gladwin AM, *et al.* Nitric oxide and prostacyclin. divergence of inhibitory effects on monocyte chemotaxis and adhesion to endothelium in vitro. *Arterioscler Thromb* 1991;11:254–60.
- 7 Leonardi-Bee J, Bath PMW, Bousser M-G, *et al.* Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. *Stroke* 2005;36:162–8.
- 8 McHutchison C, Blair GW, Appleton JP, *et al.* Cilostazol for secondary prevention of stroke and cognitive decline: systematic review and meta-analysis. *Stroke* 2020;51:2374–85.
- 9 Rajani RM, Quick S, Ruigrok SR, *et al.* Reversal of endothelial dysfunction reduces white matter vulnerability in cerebral small vessel disease in rats. *Sci Transl Med* 2018;10. doi:10.1126/scitranslmed.aam9507. [Epub ahead of print: 04 07 2018].
- 10 Hasel P, Dando O, Jiwaji Z, *et al.* Neurons and neuronal activity control gene expression in astrocytes to regulate their development and metabolism. *Nat Commun* 2017;8:15132.
- 11 Sprigg N, Gray LJ, Bath PMW, *et al.* Stroke severity, early recovery and outcome are each related with clinical classification of stroke: data from the 'Tinzaparin in Acute Ischaemic Stroke Trial' (TAIST). *J Neurol Sci* 2007;254:54–9.
- 12 Sprigg N, Gray LJ, Bath PMW, *et al.* Early recovery and functional outcome are related with causal stroke subtype: data from the tinzaparin in acute ischemic stroke trial. *J Stroke Cerebrovasc Dis* 2007;16:180–4.
- 13 Georgakis MK, Duering M, Wardlaw JM, *et al.* WMH and long-term outcomes in ischemic stroke: a systematic review and meta-analysis. *Neurology* 2019;92:e1298–e308.
- 14 DeBette S, Schilling S, Duperron M-G, *et al.* Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol* 2019;76:81–94.
- 15 McHutchison CA, Cvoro V, Makin S, *et al.* Functional, cognitive and physical outcomes 3 years after minor lacunar or cortical ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2019;90:436–43.
- 16 Wardlaw JM, DeBette S, Jokinen H, *et al.* ESO guideline on covert cerebral small vessel disease. *Eur Stroke J* 2021;6:CXI–CLXII.
- 17 Wardlaw J, Bath PMW, Doubal F, *et al.* Protocol: the lacunar intervention trial 2 (LACI-2). A trial of two repurposed licenced drugs to prevent progression of cerebral small vessel disease. *Eur Stroke J* 2020;5:297–308.
- 18 Potter G, Doubal F, Jackson C, *et al.* Associations of clinical stroke misclassification ('clinical-imaging dissociation') in acute ischemic stroke. *Cerebrovasc Dis* 2010;29:395–402.
- 19 Makin SDJ, Doubal FN, Dennis MS, *et al.* Clinically confirmed stroke with negative diffusion-weighted imaging magnetic resonance imaging: longitudinal study of clinical outcomes, stroke recurrence, and systematic review. *Stroke* 2015;46:3142–8.
- 20 Appleton JP, Woodhouse LJ, Adami A, *et al.* Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology* 2020;94:e439–52.
- 21 Blair GW, Appleton JP, Law ZK, *et al.* Preventing cognitive decline and dementia from cerebral small vessel disease: the LACI-1 trial. protocol and statistical analysis plan of a phase IIa dose escalation trial testing tolerability, safety and effect on intermediary endpoints of isosorbide mononitrate and cilostazol, separately and in combination. *Int J Stroke* 2018;13:530–8.
- 22 Appleton JP, Blair GW, Flaherty K, *et al.* Effects of isosorbide mononitrate and/or cilostazol on hematological markers, platelet function, and hemodynamics in patients with lacunar ischaemic stroke: safety data from the lacunar Intervention-1 (LACI-1) trial. *Front Neurol* 2019;10:723.
- 23 Blair GW, Appleton JP, Flaherty K, *et al.* Tolerability, safety and intermediary pharmacological effects of cilostazol and isosorbide mononitrate, alone and combined, in patients with lacunar ischaemic stroke: the lacunar Intervention-1 (LACI-1) trial, a randomised clinical trial. *EClinicalMedicine* 2019;11:34–43.
- 24 Blair GW, Janssen E, Stringer MS, *et al.* Effects of cilostazol and isosorbide mononitrate on cerebral hemodynamics in the LACI-1 randomized controlled trial. *Stroke* 2022;53:29–33.
- 25 Gamble C, Krishan A, Stocken D, *et al.* Guidelines for the content of statistical analysis plans in clinical trials. *JAMA* 2017;318:2337–43.
- 26 Hemming K, Kearney A, Gamble C, *et al.* Prospective reporting of statistical analysis plans for randomised controlled trials. *Trials* 2020;21:898.
- 27 MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *The Lancet* 2001;357:455–62.
- 28 Clancy U, Gilmartin D, Jochems ACC, *et al.* Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. *Lancet Psychiatry* 2021;8:225–36.
- 29 Jackson CA, Hutchison A, Dennis MS, *et al.* Differing risk factor profiles of ischemic stroke subtypes: evidence for a distinct lacunar arteriopathy? *Stroke* 2010;41:624–9.
- 30 Jiménez-Sánchez L, Hamilton OKL, Clancy U, *et al.* Sex differences in cerebral small vessel disease: a systematic review and meta-analysis. *Front Neurol* 2021;12:756887.
- 31 Del Bene A, Makin SDJ, Doubal FN, *et al.* Variation in risk factors for recent small subcortical infarcts with infarct size, shape, and location. *Stroke* 2013;44:3000–6.
- 32 Staals J, Makin SDJ, Doubal FN, *et al.* Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology* 2014;83:1228–34.

LACI-2 SAP V1.5

06/06/2022

SUPPLEMENT – LACunar Intervention Trial 2 (LACI-2) Statistical Analysis Plan**SECTION 1. ADMINISTRATIVE INFORMATION****1 Title and trial registration****1a Title:** Lacunar Intervention Trial 2**Acronym:** LACI-2**1b Registration:** ISRCTN14911850; IRAS project number: 206480**2 SAP version:** 1.5 (06 June 2022)**3 Protocol version:** 7.0 (14 October 2020)**4 SAP revisions****4a Revision history:**


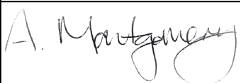

Version 1.4 to 1.5

- Text added about the planned soft database lock and analysis (section 13a).
- Text added explaining comparison of dual versus no treatment (section 27a).
- Differences and p values removed (Tables 1, 5).
- Analyses comparing dual versus no treatment do not include all four groups so cilostazol only and ISMN groups removed (Table 9).

4b Justification for each revision: N/A**4c Timing of SAP revisions:** These antedate data lock and analysis. Where there is a difference between the protocol (on website), published protocol ¹ and SAP, the SAP will take precedence.**5 Roles and responsibilities****Author:** Philip M Bath**Responsible statisticians:** Iris Mhlanga (blinded statistician), Lisa J Woodhouse (blinded statistician), Alan A Montgomery**Chief Investigator:** Joanna M Wardlaw**Contributors and roles:**

Philip M Bath, Iris Mhlanga, Lisa J Woodhouse, Fergus Doubal, Katherine Oatey, Alan A Montgomery, Joanna M Wardlaw, for the LACI-2 Investigators*

6 Signatures

| Role | Name | Signature | Date |
|-------------------------------|-----------------|--|--------------|
| 6a Author: | Philip Bath |  <small>Philip Bath (Jun 9, 2022 10:02 GMT+1)</small> | Jun 9, 2022 |
| 6b Senior statistician | Alan Montgomery |  | Jun 15, 2022 |
| 6c Chief Investigator: | Joanna Wardlaw |  | Jun 9, 2022 |

SECTION 2. INTRODUCTION**7 Background and rationale**

LACI-2 SAP V1.5

06/06/2022

Prior to analysis and presentation of the primary results, this publication presents the statistical analysis plan (SAP)^{2 3} alongside the detailed listing of baseline characteristics presented in the accompanying baseline paper. This Supporting Information Appendix S1 details the full SAP and is presented prior to locking of the study database so that analyses are not data driven or reported selectively.⁴ In addition to the SAP, we also list planned secondary analyses and substudies. The SAP follows the recommended layout.^{2 3}

8 Objectives

8a Primary Objective: To determine whether a prospective, randomised trial of cilostazol and ISMN, individually or in combination, on a background of guideline stroke prevention therapy, in lacunar ischaemic stroke is feasible in the UK, thence proceeding as seamlessly as possible to a large phase III trial.

8b Secondary Objectives: To assess drug tolerability, safety, recruitment rates and accuracy, outcome event rates and retention in preparation to a large phase III randomised controlled trial to prevent recurrent lacunar stroke and physical and cognitive impairment.

This SAP focuses on these primary and secondary objectives. Planned follow-on publications will address tertiary questions.

SECTION 3. STUDY METHODS

9 Trial design

Prospective randomised open-label blinded end-point (PROBE) partial-factorial phase IIb/c trial aiming to recruit 400 patients recruited in UK Stroke Network Centres, with follow-up to one year.

10 Randomisation: By central computer-generated allocation at the University of Nottingham with minimisation on key prognostic factors: age, sex, stroke severity (NIHSS), dependency resulting from the stroke, systolic blood pressure \leq / $>$ 140 mmHg, smoking status, time after stroke, and years of education.

11 Sample size/power considerations

Conservatively, we have used sample size calculations based on binary measures. Use of ordinal measures at the time of analysis will increase statistical power.

11a Event rates: Annual event rates (Table A) were assessed from trials (SPS3,⁵ lacunar patients in ENOS,^{6 7} IST-3^{8 9}) and observational data (LADIS;¹⁰ our¹¹⁻¹³ and other¹⁴ studies). All-cause death rates were assumed to be 2.0% with upper 95% CI of 4% in 400 patients.⁵ Hence, the sample size was set at 400 participants.

Table A Annual absolute risks (%) of outcome events after lacunar stroke

| Vascular death | Non-vascular death | Non-fatal IS or TIA | Non-fatal ICH | MI | MACE | Dependent (mRS 3-5) | Cognitive impairment | Dementia |
|----------------|--------------------|---------------------|---------------|-----|------|---------------------|----------------------|----------|
| 1.8 | 0.5 | 2.5 | 0.5 | 0.6 | 3 | 15 | 30 | 15 |

ICH: intracerebral haemorrhage; IS: ischaemic stroke; MACE: major adverse cardiac events; MI: myocardial infarction; mRS: modified Rankin scale; TIA: transient ischaemic stroke

11b Comparison of two groups in a future phase III trial: Assuming power 0.80, $\alpha=0.05$, 1:1 randomisation, composite event rate (MACE, dementia, non-vascular death, new MRI signs) 45% and absolute reduction 9% (relative risk reduction 20%), and loss to follow-up 10%, a sample size of 1100 will be needed. A

LACI-2 SAP V1.5

06/06/2022

number of outcomes are relevant to patients with SVD and using these has implications for the sample size (Table B).

Table B. Sample size for composite outcome in main trial using estimated event rates.¹

| Composite model | A | B | Ci | Cil | D |
|------------------------------------|--|-----------------------|--|-----|---|
| Composite outcome for phase III | MACE, dementia, non-vascular death, new MR signs | MACE, dementia, death | MACE, cognitive decline, dependency decline, all-cause death | | MACE, cognitive impairment, dependency, all-cause death |
| 1-beta (power) | 80% | 80% | 80% | 80% | 80% |
| Event rate, control, pa | 50% | 10% | 30% | 30% | 45% |
| Relative risk reduction | 20% | 20% | 20% | 30% | 20% |
| Event rate, active, pa | 40% | 8% | 24% | 21% | 36% |
| Total sample size | 950 | 6626 | 1784 | 778 | 976 |
| Total trial size, including losses | 1250 | 7400 | 2000 | 900 | 1100 |

MACE: major adverse cardiac events; MRI: magnetic resonance imaging

12 Framework

The primary objectives are to assess the feasibility of recruitment and adherence to medication.

13 Statistical interim analyses and stopping guidance

13a Interim analyses: Data are tabulated twice annually prior to Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) meetings. No unblinded comparative analyses will be performed until data collection has been completed and the database locked.

Prior to the final database lock, the database will be subject to a soft lock and the provisional data tabulated and analysed for review by the TSC and DMC. Any final queries will be raised and resolved prior to final database lock. Members of staff still involved in the collation of data and resolution of data queries will not attend the meeting and the data reviewed at the meeting will remain strictly confidential until the point of final database lock to avoid any bias.

13b Adjustments of significance level: There is no planned adjustment.

13c Stopping rules: There are no formal stopping rules, but the DMC have responsibility to make recommendations to pause or modify the study, should there be any safety or efficacy considerations.

14 Timing of final analyses

These will be performed once data collection has been completed and the database has been locked.

15 Timing of outcome assessments

Assessments will be performed at baseline, 1-2 weeks, 3-4 weeks, 6 and 12 months (**Table C**).

Table C. Assessments at baseline and follow-up by time point (adapted from protocol and ¹).

LACI-2 SAP V1.5

06/06/2022

| Assessment | Prior to Baseline | Visit 1 Baseline | Week 1-2 | Week 3-4 | Month 6 | Month 12 |
|--|-------------------|------------------|----------------|----------------|------------------|------------------|
| Screening for eligibility and consent [†] | X ^S | | | | | |
| Confirm and document ongoing consent | | X ^S | | | | |
| Medical including drug history | | X ^S | | | | |
| Assess MR or CT diagnostic scan; send copy to Edinburgh | | X ^S | | | | |
| Randomisation | | X ^S | | | | |
| Haematology (full blood count) and Biochemistry (urea, electrolytes, creatinine) – most recent value obtained since time of index stroke is acceptable unless clinical reason to expect change | | X ^S | | | | |
| Blood pressure | | X ^S | | | | X ^S ‡ |
| Cognitive test: document years of education; Montreal Cognitive Assessment (MOCA) | | X ^S | | | | |
| Timed Trail Making Test B | | X ^S | | | | X ^S ‡ |
| Dispense trial medication ² | | X ^S | | | X ^S | |
| Structured questionnaire: symptoms; medication history and IMP tablet adherence | | | X ^S | X ^S | X ^C | X ^C |
| Structured questionnaire: recurrent vascular events, mRS, TICS, t-MOCA, SIS, ZUNG | | | | | X ^C | X ^C |
| Obtain IQCODE (post/phone) from relative | | | | | | X ^C |
| Follow-up brain MRI | | | | | | X ^S |
| Health Economics data: EQ-5D-5L, EQ-VAS | | | | | | X ^C |
| Adverse event / con meds reporting as necessary | | | X ^S | X ^S | X ^{S,C} | X ^{S,C} |

[†] Consent will be obtained before the data collection procedures commence or randomisation is performed. Randomisation occurs at the end of the baseline visit.

[‡] at 12 months in some centres only.

² Dispensing in 3-monthly intervals is allowed.

^S Assessment performed by local site team.

^C Assessment performed by blinded assessor who is part of the central trial team.

SIS: Stroke Impact Scale; TICS: telephone interview for cognitive status; t-MOCA: telephone MOCA.

SECTION 4. STATISTICAL PRINCIPLES

LACI-2 SAP V1.5

06/06/2022

Confidence and p values**16 Level of statistical significance**

The results of analyses and comparisons will be shown with $p < 0.05$.

17 Multiplicity

No adjustment will be made for multiplicity.

18 Levels of confidence intervals

The results of analyses and comparisons will be shown with 95% confidence intervals.

19 Adherence

19a Definition: 75% of patients will be able to tolerate trial medication, in at least half dose, up to one year after randomisation (i.e. less than 25% will stop trial medication completely through inability to tolerate the drugs).

19b Adherence presentation: See Table 4.

19c Protocol deviations: Protocol violations will be reported to the sponsor within 24 hours of becoming aware of the violation. Protocol deviations will be recorded in a protocol deviation log with these submitted to the sponsors every 3 months.

19d Protocol deviation presentation: Listing of violations and deviations and their frequency.

20 Analysis populations

Three populations are defined:

1. Intention-to-treat: All consented participants with a primary outcome measure.
2. Per protocol: All consented participants with a primary outcome measure who received at least one dose of randomised medication and who had no protocol violation, e.g. they fulfilled all eligibility criteria.
3. Safety: All consented participants who received at least one dose of randomised medication.

Multiple variable analyses will include all patients with complete data for the dependent and each independent variable. All available data will be used, and missing data will not be imputed.

SECTION 5. TRIAL POPULATION**21 Screening data**

No screening logs will be kept so that data collection can be prioritised.

22 Eligibility

1. Clinical lacunar stroke syndrome.
2. Brain scanning with MR including diffusion imaging wherever possible, and obtained soon after the presentation with stroke, which showed either:
 - a. A recent, relevant (in time and location) acute small subcortical (i.e. lacunar) infarct on diffusion MR imaging.
 - b. If no visible acute small subcortical infarct on diffusion MR imaging 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);
 - c. If only a CT brain scan is available, then there is a small relevant (in time and location) subcortical (i.e. acute lacunar) 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).

LACI-2 SAP V1.5

06/06/2022

3. Age >30 years.
4. Independent in activities of daily living (modified Rankin Scale ≤ 2).
5. Capacity to give consent themselves.

23 Recruitment

Recruitment will be summarised in a CONSORT flow diagram.

24 Withdrawal/follow-up

Withdrawals, and missed follow-ups and their timing will be summarised in the CONSORT flow diagram.

25 Baseline patient characteristics

25a Baseline characteristics: These will comprise demographic, education, premorbid function, cognitive ability, medical history, blood pressure, stroke investigations, clinical and brain imaging parameters (Table 1).

25b Summarisation: Data will be shown as number (%), median [interquartile range] or mean (standard deviation) as appropriate.

SECTION 6. ANALYSIS

26 Outcome definitions

26a Specifications:

Primary endpoint

Feasibility of a Phase III efficacy trial assessed as:

- Recruitment of sufficient patients, i.e. 400 patients in 24 months in the UK (and taking account of interruption due to COVID-19).
- >95% of randomised patients are retained for follow-up at one year.

Secondary outcomes - participant

Tolerability: 75% of patients will be able to tolerate trial medication, in at least half dose, up to one year after randomisation (i.e. less than 25% will stop trial medication completely through inability to tolerate the drugs).

Safety

- Symptoms of systemic or intracranial bleeding.
- The absolute risk of death, including fatal haemorrhage, does not differ significantly, i.e. fall outside the upper 95% CI of 2% per year on trial drugs versus no trial drugs, when given in addition to guideline stroke prevention drugs.
- There are no new ischaemic or haemorrhagic brain lesions or increase in SVD lesions on one year MRI significantly (at the $p < 0.01$ level).

Efficacy

- Individual event-rates for stroke, TIA, myocardial ischaemia, cognitive impairment and dementia.
- The *combined rate* of recurrent stroke, MI, death, mild cognitive impairment (including dementia), dependency and new stroke lesions on scanning at 1 year will be 40-50% at one year after enrolment in order to allow detection of a modest but clinically-important reduction in poor outcomes in a phase III trial.
- Health economic measures include the health utility score (EQ-5D-5L) and the visual analogue score (EQVAS) at 12 months.

26b Units: Units will be shown in tables.

26c Calculations/transformations: Quality of life using UK weightings.

Brain frailty

Based on neuroimaging:

- Brain frailty = Atrophy + WML + Previous stroke lesion ⁷

LACI-2 SAP V1.5

06/06/2022

- SVD score for CT = WML, lacunes; for MRI includes WMH, lacunes, PVS and microbleeds¹⁵

Montreal cognitive assessment-modified (MoCA-m) trails

Since Trails A and B are performed, the MoCA trail is not collected but rather estimated from the Trails B score:

- If Trails B score <12 then MoCA trail = 0
- If Trails B score ≥12 then MoCA trail = 1

27 Analysis methods

27a Methods

Primary endpoint

- Tabulation and graphical presentation of participant recruitment aiming for 400 participants in 24 months.
- Tabulation of retention of participants at one year aiming for >95%.

Analyses of secondary outcomes

Tabulations of:

- Tolerability to trial medications aiming for 75% of patients taking at least half dose for up to one year after randomisation.
- Death, including fatal haemorrhage, aiming for less than outside the upper 95% CI of 2% per year.
- The *combined rate* of recurrent stroke, MI, death, cognitive impairment and dependency, aiming for 40-50% at one year after enrolment.

Comparison of rates of events between the treatment groups: cilostazol vs no cilostazol, ISMN vs no ISMN, and cilostazol and ISMN vs neither, for:

- Systemic or intracranial bleeding, recurrent cerebral and systemic vascular events, and vascular and non-vascular causes of death.
- Death, all cause.
- New ischaemic or haemorrhagic stroke lesion or increase in SVD lesions on MRI.
- Composite of: recurrent clinically-evident stroke, MI, death, cognitive impairment (including dementia) and dependency.
- Individual event: stroke (clinically-evident or imaging-detected ischaemic or haemorrhagic stroke to be reported separately), TIA, myocardial ischaemia, cognitive impairment and dementia.
- New infarcts and haemorrhages, absolute and change in WMH, microhaemorrhages, lacunes, atrophy imaging variables from central read of baseline imaging and one year MRI
- The comparisons of combined cilostazol and ISMN versus neither, whilst being very underpowered statistically, are presented since these may be the two groups studied in the planned follow-on trial.

Central tendency, comparisons and regressions will be analysed as follows (**Table D**).

Table D. Descriptive and analytical statistics

| | Binary | Nominal | Ordinal | Continuous |
|-----------------------------------|----------------------------------|--------------------------|-----------------------------------|----------------------------------|
| Central tendency and distribution | N (%) | N (%) | Median [interquartile range] | Mean (standard deviation) |
| Comparisons | Chi-square (2x2) | Chi-square (2x2, or rxc) | Mann-Whitney U or Kruskal-Wallis | t-test (pooled) or 1-way ANOVA |
| Regression | Binary logistic regression (BLR) | - | Ordinal logistic regression (OLR) | Multiple linear regression (MLR) |

27b Covariate adjustment: Analyses will be adjusted for minimisation covariates:

LACI-2 SAP V1.5

06/06/2022

- Age, sex, stroke severity (NIHSS), dependency resulting from the stroke, systolic blood pressure, smoking status, time after stroke, years of education.

Covariate adjustment with continuous variables (age, NIHSS, SBP, time after stroke, years of education) will use original, not dichotomised, data.

27c Assumption checking: The assumption of proportionality will be tested using the likelihood test.

27d Alternative methods: If the data fail the assumption of proportionality (tested using the likelihood test), we will use alternative methods such as multiple logistic regression.

27e Sensitivity analyses: In addition to assessment of raw data, the primary outcome will be analysed using additional statistical approaches in sensitivity analyses:

- Unadjusted analysis
- Imputation (multiple regression imputation) of missing data (adjusted)¹⁶

27f Subgroup analyses: The secondary endpoint of the composite of: recurrent stroke, MI, death, cognitive impairment and dependency, will be studied in:

- Pre-specified subgroups comprising the minimisation variables.
- Any other variables demonstrating imbalance at baseline.

The results of these subgroup analyses will not be adjusted for multiple testing. These analyses are planned for the phase III efficacy trial and so will be tested in the present study.

28 Missing data

Missing data may occur at outcome level or at test level or within a test at component item level. Notably, some tests have to exclude components if performed by telephone and/or postal questionnaire or require a one year MRI. There is often a relationship between inability to complete outcome assessment and cognitive function or neurological deficit after stroke (e.g. inability to hold a pen) and so assumptions around random missingness may not be valid, even if the patterns of missing data initially suggest 'missing completely at random' status. Indeed, failure to complete a test may be an indicator of cognitive impairment rather than real missingness.

The approaches taken to missing cognitive and other data can have a substantial effect on epidemiological estimates.¹⁶ We will use the approach that makes greatest use of available data.

Where in study data are not available, or participants are lost to follow-up, we have permissions to allow for linkage of the study dataset to primary and secondary care electronic health records. This will allow for an assessment of clinical outcomes across all the participants.

29 Additional analyses

Global outcomes

We will assess global outcomes integrating multiple scores into one analysis and so provide a more holistic measure and improve statistical power. We will assess global outcomes comprising:

- Recurrent ordinal stroke (clinically-evident and/or imaging-detected),¹⁷ ordinal MI, cognition (MoCA), dependency (mRS), quality of life (EQ-5D).

Analyses will use the Wei-Lachin test¹⁸⁻²¹ with comparison of data at 1 year.

Cognitive domains, based on DSM-V

We will categorise cognition into 7- and 4-level ordinal scales based on DSM-V²² categorisation (Table E).²³ We will calculate scores for cognitive domains using sub-scores of MoCA (or TICS if missing) although we recognise that these global cognitive assessments have some test items that map to a more than one domain, e.g. the

LACI-2 SAP V1.5

06/06/2022

clock drawing test in the MoCA includes aspects of attention, executive function and visual-perceptual function.

- Learning and memory: orientation in place (from MoCA), delayed recall of five word (MoCA), and recall and delayed recall of ten words (TICS)
- Language: using comprehension, semantic and recent memory (from MoCA; similar elements in TICS-M)
- Perceptual-motor function: Cube copy and clock drawing from MoCA
- Executive function: Trail making tests A & B, verbal fluency test (VFT-phonemic)-F (from MoCA); verbal fluency test (VFT-semantic)-animals; clock drawing test (from MoCA); digits forward (from MoCA); digits backward (from MoCA)
- Complex attention: using serial sevens subtraction (MoCA), letter tapping (MoCA)
- Social cognition is not classically assessed in cognitive screening tools and there are no agreed generic short form assessments for social cognition. Aspects of social cognition will be assessed through informant data and NPI-Q although these are not part of the core outcome set.

Table E. Categorisation of cognition based on DSM V with operationalisation (adapted summary from ²³).

| | Seven-level categorisation and operationalisation | Four-level categorisation and operationalisation |
|--|--|---|
| Normal cognition | No evidence of cognitive impairment (T-MoCA:20-22 AND TICS-m: 25-39) | No evidence of cognitive impairment (T-MoCA:20-22 AND TICS-m: 25-39) |
| Minor Neurocognitive disorder (mild cognitive impairment) | Single domain Scores are reduced by > 1 point in only one cognitive domain of T-MoCA | Evidence of cognitive impairment (T-MoCA: 15-19 OR TICS-m: 17-24) AND |
| | Multi-domain Scores are reduced by > 1 point in more than one cognitive domain of T-MoCA | No evidence of functional impairment (mRS <2 OR no change in mRS if pre-stroke mRS >1) |
| Major neurocognitive disorder | Mild cognitive impairments (T-MoCA 15-19 OR TICS-m 17-23) AND Mild dysfunction (mRS <3) | Persisting cognitive impairment (T-MoCA score <19 OR TICS-m <24 on more than one follow-up) AND Functional impairment (mRS ≥2 or IQCODE >3.6 at final follow-up) |
| | Moderate cognitive impairments (T-MoCA 10-14 OR TICS-m 12-16) AND Moderate dysfunction (mRS 3 or 4) | OR |
| | Severe cognitive impairments (T-MoCA <10 OR TICS-m <12) AND Severe dysfunction | Any clinical diagnosis of dementia made independent of study, e.g. by memory clinic, in primary care, recording of dementia on death certification, prescription of cholinesterase inhibitor or memantine |

LACI-2 SAP V1.5

06/06/2022

| | | |
|--------------|---------------------------|---------------|
| | In a care-home OR mRS 4,5 | |
| Death | Death (mRS 6) | Death (mRS 6) |

30 Harms

These are presented as serious adverse events in Tables 6a-c and 7a-c.

31 Statistical software

Statistical Analysis System (SAS) version 9.4, SAS Institute Incorporation, Cary, North Carolina.

SECTION 7. ADDITIONAL INFORMATION

Confounding covariates

The primary outcome is recruitment, and this will be tabulated; as such, there are no confounding covariates.

The possible primary outcome in any following trial will likely be a composite comprising MACE, dementia or mild cognitive impairment, non-vascular death and new MRI signs and these event rates will be assessed in the current trial. The components are likely to be correlated. Example confounding variables are given and these are categorised by whether these were 'measured', as per routine practice, or 'unmeasured'; the latter will lead to residual confounding.

Composite outcome

Measured variables: Age, highest educational attainment, main occupation, socioeconomic status, stroke severity, function at randomisation, cognitive ability at randomisation, diabetes mellitus, hypertension, smoking, carotid disease, blood pressure, prescribed medications, time from stroke to randomisation, presence of a relevant infarct and SVD lesion severity on brain imaging.

Unmeasured: Examples are social isolation, vision, hearing, cardiac function (atrial fibrillation and heart failure are documented) and post-stroke complications.

Governance

LACI-2 is funded by the British Heart Foundation (CS/15/5/31475) and approved by the East Midlands – Nottingham 2 Research Ethics Committee (Ref: 17/EM/0077). The Sponsor is the ACCORD office, University of Edinburgh and NHS Lothian. NHS Research and Development/ Innovation approval is given at each participating site. The study is adopted by the National Institute for Health Research (NIHR) Clinical Research Network in England and the Stroke Research Network in Scotland.

Minimising bias

Multiple approaches are taken to minimise bias: central data registration with real-time on-line validation; minimisation at randomisation; blinded central postal and/or telephone assessment of outcomes; blinded adjudication of neuroimaging; inclusion of patients enrolled in other studies (co-enrolment) where feasible; analysis by intention-to-enrol (i.e. all participants) and in pre-specified subgroups.

Publications, published and planned

1. Protocol - published
2. SAP and baseline data - this publication
3. Primary results paper
4. Other secondary publications as determined by the Trial Steering Committee

LACI-2 SAP V1.5

06/06/2022

Data sharing

In the future, the anonymised study data will be made available for use by external investigators in appropriate analyses upon request via a publicly accessible portal (e.g. University of Edinburgh data share). Data from LACI-2 will also be shared as appropriate with individual patient data pooling projects involving stroke and dementia; a non-inclusive list includes:

- The Cerebrovascular diseases database, Edinburgh (<https://www.ed.ac.uk/clinical-sciences/edinburgh-imaging/research/themes-and-topics/analysis-and-processing/image-databanks/cerebrovascular-diseases-image-databank>)
- Dementia Platform UK data portal (<https://www.dementiasplatform.uk/>)
- Virtual International Stroke Trials Archive-Cognition (VISTA-COG)
- Virtual International Cardiovascular and Cognitive Trials Archive (VICCTA, <http://www.virtualtrialsarchives.org>)
- META-VCI Map (<https://metavcimap.org/>)
- STROKOG (<https://cheba.unsw.edu.au/consortia/strokog>)

Similarly, anonymised neuroimaging data will be published.²⁴ The mechanisms and processes for managing external access will be determined during the course of the study. Proposals will be considered by the LACI-2 Trial Steering Committee.

LACI-2 SAP V1.5

06/06/2022

ABBREVIATIONS

| Abbreviation | Full Text |
|---------------------|---|
| CI | Confidence Interval |
| cSVD | Cerebral small vessel disease |
| CT | Computed Tomography |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| EQVAS | EuroQol-Visual Analogue Scale |
| EQ-5D-5L | EuroQoL- 5 Dimension- 5 Level quality of life questionnaire |
| F/T | Full Time |
| ICH | Intracerebral Haemorrhage |
| IMP | Investigational Medicinal Product |
| IS | Ischaemic Stroke |
| ISMN | Isosorbide Mononitrate |
| LACI-2 | Lacunar Intervention Trial-2 |
| LACS | lacunar syndrome |
| LVH | left ventricular hypertrophy |
| MACE | Major Adverse Cardiac Events |
| MI | Myocardial Infarction |
| MOCA | Montreal Cognitive Assessment |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin scale |
| NIHSS | National Institutes Health Stroke Scale |
| NO | Nitric oxide |
| PACS | Partial Anterior Circulation Syndrome; |
| PROBE | Prospective Randomised Open-label Blinded-Endpoint |
| PGI2 | Prostacyclin |
| POCS | Posterior Circulation Syndrome |
| P/T | Part Time |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SBP | Systolic Blood Pressure |
| SIS | Stroke Impact Scale |
| SVD | Small vessel disease |
| TACS | Total Anterior Circulation Syndrome |
| TIA | Transient Ischaemic Attack |
| TICS | Telephone Interview for Cognitive Status |
| t-MOCA | Telephone MOCA |
| TSC | Trial Steering Committee |
| WMH | White Matter Hyperintensity |

LACI-2 SAP V1.5

06/06/2022

REFERENCES

1. Wardlaw J, Bath PMW, Doubal F, et al. Protocol: The Lacunar Intervention Trial 2 (LACI-2). A trial of two repurposed licenced drugs to prevent progression of cerebral small vessel disease. *Eur Stroke J* 2020;5(3):297-308. doi: 10.1177/2396987320920110 [published Online First: 20200420]
2. Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA* 2017;318(23):2337-43. doi: 10.1001/jama.2017.18556
3. Hemming K, Kearney A, Gamble C, et al. Prospective reporting of statistical analysis plans for randomised controlled trials. *Trials* 2020;21(1):898. doi: 10.1186/s13063-020-04828-8 [published Online First: 20201028]
4. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet* 2001;357(9254):455-62. doi: 10.1016/s0140-6736(00)04017-4 [published Online First: 2001/03/29]
5. SPS3 Investigators BO, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *New England Journal of Medicine* 2012;376(9):817-25. doi: 10.1056/NEJMoa1204133
6. Bath PM, Woodhouse L, Scutt P, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet* 2015;385(9968):617-28. doi: 10.1016/s0140-6736(14)61121-1 [published Online First: 2014/12/04]
7. Appleton JP, Woodhouse LJ, Adami A, et al. Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology* 2020;94(5):e439-e52. doi: 10.1212/WNL.0000000000008881 [published Online First: 2019/12/27]
8. Sandercock P, Wardlaw JM, Lindley RI, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012;379(9834):2352-63. doi: 10.1016/S0140-6736(12)60768-5 [published Online First: 20120523]
9. Sandercock P, Wardlaw JM, Dennis M, et al. Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial IST-3): 18-month follow-up of a randomised controlled trial. *Lancet Neurology* 2013;12(8):768-76. doi: 10.1016/s1474-4422(13)70130-3
10. Schmidt R, Berghold A, Jokinen H, et al. White matter lesion progression in LADIS: frequency, clinical effects, and sample size calculations. *Stroke* 2012;43(10):2643-7. doi: 10.1161/strokeaha.112.662593 [published Online First: 2012/08/11]
11. McHutchison CA, Cvorov V, Makin S, et al. Functional, cognitive and physical outcomes 3 years after minor lacunar or cortical ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2019;90(4):436-43. doi: 10.1136/jnnp-2018-319134 [published Online First: 20181215]
12. Wardlaw JM, Doubal FN, Valdes-Hernandez M, et al. Blood-brain barrier permeability and long-term clinical and imaging outcomes in cerebral small vessel disease. *Stroke* 2013;44(2):525-7. doi: 10.1161/strokeaha.112.669994 [published Online First: 2012/12/13]
13. Chappell FM, Del Carmen Valdés Hernández M, Makin SD, et al. Sample size considerations for trials using cerebral white matter hyperintensity progression as an intermediate outcome at 1 year after mild stroke: results of a prospective cohort study. *Trials* 2017;18(1):78. doi: 10.1186/s13063-017-1825-7 [published Online First: 20170221]
14. Pavlovic AM, Pekmezovic T, Tomic G, et al. Baseline predictors of cognitive decline in patients with cerebral small vessel disease. *Journal of Alzheimer's disease : JAD* 2014;42 Suppl 3:S37-43. doi: 10.3233/JAD-132606

LACI-2 SAP V1.5

06/06/2022

15. Staals J, Makin SD, Doubal FN, et al. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology* 2014;83(14):1228-34. doi: 10.1212/WNL.0000000000000837 [published Online First: 20140827]
16. Lees RA, Hendry Ba K, Broomfield N, et al. Cognitive assessment in stroke: feasibility and test properties using differing approaches to scoring of incomplete items. *Int J Geriatr Psychiatry* 2017;32(10):1072-78. doi: 10.1002/gps.4568 [published Online First: 2016/08/16]
17. Bath PM, Woodhouse LJ, Appleton JP, et al. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. *Lancet* 2018;391(10123):850-59. doi: 10.1016/s0140-6736(17)32849-0 [published Online First: 2017/12/25]
18. Lachin J. Applications of the Wei-Lachin multivariate one-sided test for multiple outcomes on possibly different scales. *PLoS One* 2014;9(10) doi: 10.1371/journal.pone.0108784
19. Muresanu D, Heiss W, Hoernberg V, et al. Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial. *Stroke* 2016;47(1):151-9. doi: 10.1161/STROKEAHA.115.009416 [published Online First: 12 Nov 2015]
20. Appleton J, Scutt P, Sprigg N, et al. Hypercholesterolaemia and vascular dementia. *Clinical Sciences* 2017;131(14):1561-78. doi: 10.1042/CS20160382 [published Online First: 21 March 2017]
21. Bath PM, Woodhouse LJ, Krishnan K, et al. Prehospital Transdermal Glyceryl Trinitrate for Ultra-Acute Intracerebral Hemorrhage: Data From the RIGHT-2 Trial. *Stroke* 2019;50(11):3064-71. doi: 10.1161/STROKEAHA.119.026389 [published Online First: 2019/10/07]
22. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nature reviews Neurology* 2014;10(11):634-42. doi: 10.1038/nrneurol.2014.181 [published Online First: 2014/09/30]
23. Wardlaw JM, Doubal F, Brown R, et al. Rates, risks and routes to reduce vascular dementia (R4vad), a UK-wide multicentre prospective observational cohort study of cognition after stroke: Protocol. *European Stroke Journal* 2021;6(1):89-101. doi: 10.1177/2396987320953312
24. Wardlaw J, Bath P, Sandercock P, et al. The NeuroGrid stroke exemplar clinical trial protocol. *International Journal of Stroke* 2007;2:63-9.

LACI-2 SAP V1.5

06/06/2022

Main paper tables**Table 1. Baseline characteristics by treatment group isosorbide mononitrate (ISMN), cilostazol (Cil) or both (ISMN+Cil).**

Data are number (%), median [interquartile range] or mean (standard deviation).

| | N | All | ISMN | No ISMN | Cil | No Cil | ISMN + Cil | ISMN only | Cil only | Neither |
|---------------------------------|----------|------------|-------------|----------------|------------|---------------|-------------------|------------------|-----------------|----------------|
| N | XX | XX | XX | XX | XX | XX | XX | XX | XX | XX |
| Demographics | | | | | | | | | | |
| Age (yr) † | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <=70 years | XX | XX (X) | XX (X) | XX (X) | XX | XX (X) | XX | XX (X) | XX (X) | XX (X) |
| Sex, female (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| modified Rankin Scale >1 (%) † | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Onset to randomisation (days) † | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <= 100 days | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Age completing education (yr) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Highest education (%) † | | | | | | | | | | |
| Primary | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Secondary | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| O' level/GCSE | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| A' level | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Undergraduate degree | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Postgraduate degree | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Lifestyle | | | | | | | | | | |
| Smoking † | | | | | | | | | | |
| Current | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Past | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Never | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| History (%) | | | | | | | | | | |
| Hypertension, drug treated | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Hyperlipidaemia, drug treated | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Diabetes mellitus | | | | | | | | | | |
| Oral agents | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Insulin | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Atrial fibrillation | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Heart failure | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Previous stroke | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Previous TIA | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |

LACI-2 SAP V1.5

06/06/2022

| | | | | | | | | | | |
|------------------------------|----|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Family history, young stroke | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Medications | | | | | | | | | | |
| Anticoagulants | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Antibiotics | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Antihypertensives | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Antiplatelets | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Lipid-lowering | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Proton pump inhibitor | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| PDE5 inhibitor | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Other drugs | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| No. medications /day | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Grapefruit juice (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Clinical (%) | | | | | | | | | | |
| Systolic BP (mmHg) † | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Diastolic BP mmHg) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Atrial fibrillation | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| NIHSS (/42) † | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Weakness, Side (%) | | | | | | | | | | |
| right | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| left | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| both | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Sensory loss (%) | | | | | | | | | | |
| Right | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Left | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| both | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Ataxia (%) | | | | | | | | | | |
| left | XX | XX (X) | XX (X) | XX (X) | XX | XX (X) | XX (X) | XX (X) | XX | XX (X) |
| right | XX | XX (X) | XX (X) | XX (X) | XX | XX (X) | XX (X) | XX (X) | XX | XX (X) |
| Neglect/inattention (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Dysphasia (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Dysarthria (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Visual loss (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Cognition | | | | | | | | | | |
| MoCA | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| MoCA <=24 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Verbal fluency F, <11 words | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Trails B, time | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Trails B, points | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Investigations | | | | | | | | | | |
| CT scan | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| MRI Scan | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Both scans | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Stroke-CT scan (days) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Stroke-MRI scan (days) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |

LACI-2 SAP V1.5

06/06/2022

| | | | | | | | | | | |
|---------------------------------------|----|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Index infarct present (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Index infarct side, left (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| cSVD moderate/severe (%) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| WMH/ hypoattenuations | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Carotid stenosis | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Left >=50% | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Right >=50% | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| ECG, (%) | | | | | | | | | | |
| Sinus | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| AF | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Haemoglobin (g/l) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Creatinine (µmol/l) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| eGFR (ml/min) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Contraindications to treatment | | | | | | | | | | |
| ISMN | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Cilostazol | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |

† Minimisation variable

ECG: electrocardiogram; F/T: full time; ICH: intracerebral haemorrhage; IS: ischaemic stroke; LACS: lacunar syndrome; LVH: left ventricular hypertrophy; PACS; partial anterior circulation syndrome; POCS: posterior circulation syndrome; P/T: part time; TACS: total anterior circulation syndrome; TIA: transient ischaemic attack

LACI-2 SAP V1.5

06/06/2022

Table 2. Feasibility measures.

Data are number (%).

| Measure | Metric | Achieved |
|--------------------------------------|--------------------------------|--------------------|
| Primary | | |
| Recruitment | 400 patients | 363/400 (90.8%) |
| Retention of enrolees at 1 year | >95% | XX (X) |
| Secondary | | |
| Tolerability | >=75% on at least half dose | XX (X) |
| ISMN alone | | XX (X) |
| Cilostazol alone | | XX (X) |
| Both ISMN and cilostazol | | XX (X) |
| Safety | | |
| Symptomatic extracranial bleeding | | XX (X) |
| Symptomatic intracranial bleeding | | XX (X) |
| Death | <2% | XX (X) |
| Stroke | | XX (X) |
| Haemorrhage | | XX (X) |
| Extracranial | | XX (X) |
| Intracranial | | XX (X) |
| Efficacy | | |
| Stroke | | XX (X) |
| TIA | | XX (X) |
| Myocardial infarction | | XX (X) |
| Cognitive impairment | | XX (X) |
| Dependency, mRS>2 | | XX (X) |
| Any of these | 40-50% | XX (X) |

LACI-2 SAP V1.5

06/06/2022

Table 3. Clinical Outcomes at 12 months.

Data are number (%), median [interquartile range] or mean (standard deviation). Analyses performed using binary logistic regression (BLR), ordinal logistic regression (OLR) or multiple linear regression (MLR) with adjustment for age, sex, time from stroke onset to randomisation, years of education, smoking status, and baseline mRS (dependency), stroke severity (NIHSS) and systolic blood pressure. Mean (SD) and MLR will be used instead of median [IQR] and OLR for ordinal scales with more than 7 levels (central limit theorem/large sample). The Wei-Lachin test is used to analyse multiple outcomes in parallel.

| | ISMN | No ISMN | Difference (p) | Cilostazol | No cilostazol | Difference (p) | ISMN + Cil | Neither | Difference (p) |
|----------------------|-------------|----------------|-----------------------|-------------------|----------------------|-----------------------|-------------------|----------------|-----------------------|
| Number | | | | | | | | | |
| Composite | | | CPHR | | | CPHR | | | CPHR |
| Stroke | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| TIA | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| MI | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| Cognitive impairment | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| Dependency, mRS>2 | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| Death | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| Cognition | | | | | | | | | |
| Cognition, 7 level | | | OLR | | | OLR | | | OLR |
| Normal | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Minor, single domain | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Minor, multi-domain | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Major, mild | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |

| LACI-2 SAP V1.5 | 06/06/2022 | | | | | | | | |
|----------------------------------|------------|--------|-----|--------|--------|-----|--------|--------|-----|
| Major, moderate | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Major, severe | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Death | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Cognition, 4 level Normal | XX (X) | XX (X) | OLR | XX (X) | XX (X) | OLR | XX (X) | XX (X) | OLR |
| Minor | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Dementia | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Death | XX (X) | XX (X) | | XX (X) | XX (X) | | XX (X) | XX (X) | |
| Memory/thinking problem | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| MoCA | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| TICS-m | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| Verbal fluency, animal naming | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| Trails B, time | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| Trails B, points | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| Dementia, clinical diagnosis | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| Clinical | | | | | | | | | |
| Systolic BP (mmHg) | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| Diastolic BP (mmHg) | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |

| LACI-2 SAP V1.5 | 06/06/2022 | | | | | | | | |
|---------------------|------------|--------|-----|--------|--------|-----|--------|--------|-----|
| Heart rate (bpm) | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| mRS | XX (X) | XX (X) | OLR | XX (X) | XX (X) | OLR | XX (X) | XX (X) | OLR |
| Disposition | XX (X) | XX (X) | OLR | XX (X) | XX (X) | OLR | XX (X) | XX (X) | OLR |
| ZDS | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| Clinical depression | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR | XX (X) | XX (X) | BLR |
| EQ-5D-5L, as HU | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| EQ-VAS | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| SIS | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR | XX (X) | XX (X) | MLR |
| Global | XX (X) | XX (X) | WLT | XX (X) | XX (X) | WLT | XX (X) | XX (X) | WLT |

BP: blood pressure; MoCA: Montreal cognitive assessment-modified; mRS: modified Rankin Scale; SIS: stroke impact scale; TICS-m: Telephone interview cognitive status- modified; ZDS: Zung depression scale

Global: Recurrent ordinal stroke,¹⁷ ordinal MI, cognition (MoCA), dependency (mRS), stroke impact scale, quality of life (EQ-5D).

LACI-2 SAP V1.5

06/06/2022

Table 4. Adherence to medication with at least half dose or more by randomised group: isosorbide mononitrate (ISMN), cilostazol (Cil) and both together.

| Week | ISMN | No ISMN | p | Cilostazol | No cilostazol | p | ISMN +Cil | ISMN alone | Cil only | Neither | p |
|------|--------|---------|--------|------------|---------------|--------|--------------|------------|----------|---------|--------|
| 1-2 | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | XX (X) | XX (X) | Chi-sq |
| 3-4 | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | XX (X) | XX (X) | Chi-sq |
| 26 | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | XX (X) | XX (X) | Chi-sq |
| 52 | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | Chi-sq | XX (X) | XX (X) | XX (X) | XX (X) | Chi-sq |

A more detailed table by strata of drug adherence (i.e. 25%, 50%, 75% and 100% adherence) will also be prepared.

LACI-2 SAP V1.5

06/06/2022

Table 5. Adjudicated baseline imaging characteristics by randomised group: isosorbide mononitrate (ISMN), cilostazol (Cil) and both together.

Data are number (%), median [IQR], or mean (standard deviation).

| | N | All | ISMN | No ISMN | Cil | No Cil | ISMN + Cil | ISMN only | Cil only | None |
|--|----------|------------|-------------|----------------|------------|---------------|-------------------|------------------|-----------------|-------------|
| Patients randomised | XX | XX | XX | XX | XX | XX | XX | XX | XX | XX |
| Scan | | | | | | | | | | |
| <i>Scan type(%)</i> | | | | | | | | | | |
| CT | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Time to scan (days) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| MR | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Time to scan (days) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Scan quality (%) | | | | | | | | | | |
| Good | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Moderate | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Poor | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Index Lesion (i.e. main cause of stroke symptoms) (%) | | | | | | | | | | |
| Normal Scan | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Lesion present (type) | | | | | | | | | | |
| Primary Acute ischaemia | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Primary haemorrhage | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Mimic | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| No visible | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Infarct side of brain | | | | | | | | | | |
| Right | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Left | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Both | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Location (%) | | | | | | | | | | |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | Cil | No Cil | ISMN + Cil | ISMN only | Cil only | None |
|---|----------|------------|-------------|----------------|------------|---------------|-------------------|------------------|-----------------|-------------|
| <i>Index small subcortical (i.e. acute lacunar) infarct</i> | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Internal capsule | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| External capsule | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Lentiform nucleus | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Internal border zone | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Centrum semiovale | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Thalamus | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Lacunar- small deep cerebellar lesion | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Lacunar- small deep brainstem lesion (Pons) | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Lacunar - Medulla | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Non-small subcortical (i.e. large artery cortical or large subcortical or posterior circulation) infarct | | | | | | | | | | |
| MCA territory | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| PCA territory | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Infarct size (mm) | | | | | | | | | | |
| A/P | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| R/L | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Cranio-caudal | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Microhaemorrhage (%) | | | | | | | | | | |
| Microhaemorrhages | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>No. microhaemorrhages (%)</i> | | | | | | | | | | |
| 1 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 2 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 3 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 4 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| >= 5 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Type of microhaemorrhages (%)</i> | | | | | | | | | | |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | Cil | No Cil | ISMN + Cil | ISMN only | Cil only | None |
|---|----------|------------|-------------|----------------|------------|---------------|-------------------|------------------|-----------------|-------------|
| Lobar | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Deep | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Both | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Superficial siderosis present | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Siderosis focal | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Siderosis disseminated | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Siderosis location</i> | | | | | | | | | | |
| Left | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Right | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Both | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Atrophy | | | | | | | | | | |
| Brain tissue volume reduction | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Central brain tissue volume | | | | | | | | | | |
| Modest | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Severe | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Cortical brain tissue volume | | | | | | | | | | |
| Modest | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Severe | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| White Matter hyperintensities (%) | | | | | | | | | | |
| White matter hyperintensities | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Anterior white matter lucency</i> | | | | | | | | | | |
| Restricted region adjoining ventricles | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Covering ventricle to cortex | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Posterior white matter lucency</i> | | | | | | | | | | |
| Restricted region adjoining ventricles | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Covering ventricle to cortex | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Anterior and/or Posterior white matter lucency</i> | | | | | | | | | | |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | Cil | No Cil | ISMN + Cil | ISMN only | Cil only | None |
|--|----------|------------|-------------|----------------|------------|---------------|-------------------|------------------|-----------------|-------------|
| Restricted region adjoining ventricles | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Covering ventricle to cortex | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Periventricular WMH Fazekas score</i> | | | | | | | | | | |
| 1 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 2 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 3 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Deep WMH Fazekas score</i> | | | | | | | | | | |
| 1 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 2 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 3 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Periventricular and/or Deep WMH Fazekas score</i> | | | | | | | | | | |
| 1 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 2 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 3 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Enlarged perivascular spaces (%) | | | | | | | | | | |
| Enlarged perivascular spaces | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Basal ganglia rating, worse side</i> | | | | | | | | | | |
| <=10 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 11-20 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 20-40 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| >40 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Centrum semiovale rating, worse side</i> | | | | | | | | | | |
| <=10 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 11-20 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 20-40 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| >40 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Old vascular lesions (%) | | | | | | | | | | |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | Cil | No Cil | ISMN + Cil | ISMN only | Cil only | None |
|---|----------|------------|-------------|--------------------|------------|-------------------|---------------------------|----------------------|---------------------|-------------|
| Old vascular lesions | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Old cortical infarct | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Old striatocapsular infarct | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Old borderzone infarct | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Old lacunar infarct | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Number of lacunes (%)</i> | | | | | | | | | | |
| 1 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 2 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 3 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| 4 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| >=5 | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Old brainstem/cerebellar infarcts | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Probable old haemorrhage | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Non-stroke lesions (%) | | | | | | | | | | |
| Non-stroke lesion | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| <i>Classification of non-stroke (%)</i> | | | | | | | | | | |
| Cerebral tumour | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Aneurysm | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Vascular malformation | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |
| Other non-stroke classification | XX | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) | XX (X) |

LACI-2 SAP V1.5

06/06/2022

Table 6a. Serious adverse events for ISMN.

Data are number (%).

| Number | All | | | Fatal | | |
|---------------------|-----------|-----------|----------------|-----------|-----------|----------------|
| | ISMN | No ISMN | Difference (p) | ISMN | No ISMN | Difference (p) |
| Treatment | | | | | | |
| During | xx (xx.x) | xx (xx.x) | BLR | xx (xx.x) | xx (xx.x) | BLR |
| After | xx (xx.x) | xx (xx.x) | BLR | | | BLR |
| Relationship | | | | | | |
| Possibly | xx (xx.x) | xx (xx.x) | Ch sq | xx (xx.x) | xx (xx.x) | Ch sq |
| Probably | xx (xx.x) | xx (xx.x) | - | xx (xx.x) | xx (xx.x) | - |
| Definitely | xx (xx.x) | xx (xx.x) | - | xx (xx.x) | xx (xx.x) | - |

Table 6b. Serious adverse events for cilostazol.

Data are number (%).

| Number | All | | | Fatal | | |
|---------------------|------------|---------------|----------------|------------|---------------|----------------|
| | Cilostazol | No Cilostazol | Difference (p) | Cilostazol | No Cilostazol | Difference (p) |
| Treatment | | | | | | |
| During | xx (xx.x) | xx (xx.x) | BLR | xx (xx.x) | xx (xx.x) | BLR |
| After | xx (xx.x) | xx (xx.x) | BLR | xx (xx.x) | xx (xx.x) | BLR |
| Relationship | | | | | | |
| Possibly | xx (xx.x) | xx (xx.x) | Ch sq | xx (xx.x) | xx (xx.x) | Ch sq |
| Probably | xx (xx.x) | xx (xx.x) | - | xx (xx.x) | xx (xx.x) | - |
| Definitely | xx (xx.x) | xx (xx.x) | - | xx (xx.x) | xx (xx.x) | - |

Table 6c. Serious adverse events for combined ISMN and cilostazol.

Data are number (%).

| Number | All | | | Fatal | | |
|---------------------|-----------|-------------|----------------|-----------|-------------|----------------|
| | ISMN /cil | No ISMN/cil | Difference (p) | ISMN /cil | No ISMN/cil | Difference (p) |
| Treatment | | | | | | |
| During | xx (xx.x) | xx (xx.x) | BLR | xx (xx.x) | xx (xx.x) | BLR |
| After | xx (xx.x) | xx (xx.x) | BLR | xx (xx.x) | xx (xx.x) | BLR |
| Relationship | | | | | | |
| Possibly | xx (xx.x) | xx (xx.x) | Ch sq | xx (xx.x) | xx (xx.x) | Ch sq |
| Probably | xx (xx.x) | xx (xx.x) | - | xx (xx.x) | xx (xx.x) | - |
| Definitely | xx (xx.x) | xx (xx.x) | - | xx (xx.x) | xx (xx.x) | - |

LACI-2 SAP V1.5

06/06/2022

Table 7a. Participants with at least one serious adverse events by organ randomised to isosorbide mononitrate (ISMN) versus none.

Data are number (%); comparison by binary logistic regression.

| | ISMN | All No ISMN | Difference (p) | ISMN | Fatal No ISMN | Difference (p) |
|----------------------------|--------------|--------------|--------------------------|--------------|---------------|--------------------------|
| Number | | | | | | |
| Cardiovascular | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Myocardial infarction | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Nervous system | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Ischaemic stroke | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Transient ischaemic attack | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Intracerebral haemorrhage | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Respiratory | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Gastrointestinal | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Genitourinary | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Secondary | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Haematological | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Metabolic/endocrine | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Musculoskeletal | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Infection/sepsis | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Tumour/malignancy | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Other | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Total | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |

LACI-2 SAP V1.5

06/06/2022

Table 7b. Participants with at least one serious adverse events by organ randomised to cilostazol (Cil) versus none.

Data are number (%); comparison by binary logistic regression.

| | All | | | Fatal | | |
|----------------------------|--------------|--------------|--------------------------|--------------|--------------|--------------------------|
| | Cil | No Cil | Difference (p) | Cil | No Cil | Difference (p) |
| Number | | | | | | |
| Cardiovascular | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Myocardial infarction | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Nervous system | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Ischaemic stroke | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Transient ischaemic attack | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Intracerebral haemorrhage | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Respiratory | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Gastrointestinal | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Genitourinary | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Secondary | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Haematological | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Metabolic/endocrine | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Musculoskeletal | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Infection/sepsis | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Tumour/malignancy | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Other | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Total | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |

LACI-2 SAP V1.5

06/06/2022

Table 7c. Participants with at least one serious adverse events by organ randomised to combined isosorbide mononitrate (ISMN) and cilostazol (Cil) versus neither.

Data are number (%); comparison by binary logistic regression.

| | ISMN /Cil | All No ISMN /Cil | Difference (p) | ISMN /Cil | Fatal No ISMN /Cil | Difference (p) |
|-------------------------------|----------------------|-------------------------------------|---------------------------|----------------------|---------------------------------------|---------------------------|
| Number | | | | | | |
| Cardiovascular | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Myocardial infarction | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Nervous system | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Ischaemic stroke | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Transient ischaemic attack | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Intracerebral haemorrhage | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Respiratory | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Gastrointestinal | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Genitourinary | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Secondary | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Haematological | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Metabolic/endocrine | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Musculoskeletal | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Infection/sepsis | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Tumour/malignancy | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Other | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Total | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |

LACI-2 SAP V1.5

06/06/2022

Table 8. Targeted symptoms occurring at any time on treatment on isosorbide mononitrate (ISMN), cilostazol (cil) or both.

Data are number (%); comparison by binary logistic regression.

| | ISMN | No ISMN | Difference (p) | Cil | No cil | Difference (p) | ISMN /Cil | No ISMN /Cil | Difference (p) |
|---------------------------|--------------|-----------|--------------------------|--------------|--------------|--------------------------|--------------|--------------|--------------------------|
| Headache | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Palpitations | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Dizziness | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Loose stools | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Nausea | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Bleeding | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Bruising | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Falls | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |
| Stopped normal activities | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx | xx (xx.x) | xx (xx.x) | (xx.x, xx.x), p=0.xxx |

LACI-2 SAP V1.5

06/06/2022

Table 9. Adjudicated 1 year MRI imaging characteristics by randomised group: isosorbide mononitrate (ISMN), cilostazol (Cil) and both together.

Data are number (%), median [IQR], or mean (standard deviation).

| | N | All | ISMN | No ISMN | OR/MD/HR (95%CI) | p-value | Cil | No Cil | OR/MD/HR (95%CI) | p-value | ISMN + Cil | None | OR/MD/HR (95%CI) | p-value |
|---|----|--------|--------|---------|------------------|---------|--------|--------|------------------|---------|------------|--------|------------------|---------|
| Patients randomised | XX | XX | XX | XX | | | XX | XX | | | XX | XX | | |
| Scan | | | | | | | | | | | | | | |
| Time to scan (days) | XX | XX (X) | XX (X) | XX (X) | MLR | XX | XX (X) | XX (X) | MLR | XX | XX (X) | XX (X) | MLR | XX |
| Scan quality (%) | | | | | OLR | XX | | | OLR | XX | | | OLR | XX |
| Good | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| Moderate | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| Poor | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| Appearance of the index infarct now (%) | | | | | | | | | | | | | | |
| Completely cavitated - visible on T2, FLAIR and T1" | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Partially cavitated - lacy | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Partially cavitated - hole + large WMH rim | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Partially cavitated - FLAIR cavity but not=CSF | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Partially cavitated - FLAIR=WMH T2=cavity | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Partially cavitated - visible on T2 not FLAIR | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Not cavitated (WML-like) | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Disappeared | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Become visible | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Never visible | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Evidence of new stroke (%) | | | | | | | | | | | | | | |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | OR/MD/HR (95%CI) | p-value | Cil | No Cil | OR/MD/HR (95%CI) | p-value | ISMN + Cil | None | OR/MD/p-value (95%CI) |
|-----------------------------------|----|-------------|-------------|-------------|---------------------|---------|-------------|-------------|---------------------|---------|-------------|-------------|--------------------------|
| Ischaemic | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |
| Haemorrhagic | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |
| Microhaemorrhages (%) | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |
| <i>No. microhaemorrhages (%)</i> | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| 1 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| 2 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| 3 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| 4 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| >= 5 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Change from baseline | XX | XX [XX, XX] | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR XX |
| Small vessel disease score | | | | | | | | | | | | | |
| Total | XX | XX [XX, XX] | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR XX |
| Change from baseline | XX | XX [XX, XX] | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR XX |
| Atrophy | | | | | | | | | | | | | |
| Brain tissue volume reduction | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |
| Central brain tissue volume | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| Modest | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Severe | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Cortical brain tissue volume | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| Modest | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Severe | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Change from baseline | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| More | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Less | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| None | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | OR/MD/HR (95%CI) | p-value | Cil | No Cil | OR/MD/HR (95%CI) | p-value | ISMN + Cil | None | OR/MD/HR (95%CI) | p-value |
|---|----|-------------|-------------|-------------|------------------|---------|-------------|-------------|------------------|---------|-------------|-------------|------------------|---------|
| White Matter hyperintensities (%) | | | | | | | | | | | | | | |
| White matter hyperintensities | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| <i>Anterior white matter lucency</i> | | | | | | | | | | | | | | |
| Restricted region adjoining ventricles | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Covering ventricle to cortex | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| <i>Posterior white matter lucency</i> | | | | | | | | | | | | | | |
| Restricted region adjoining ventricles | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Covering ventricle to cortex | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| <i>Anterior and/or Posterior white matter lucency</i> | | | | | | | | | | | | | | |
| Restricted region adjoining ventricles | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Covering ventricle to cortex | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| <i>Periventricular WMH Fazekas score</i> | | | | | | | | | | | | | | |
| | | | | | OLR | XX | | | OLR | XX | | | OLR | XX |
| 1 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 2 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 3 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| Change from baseline | XX | XX [XX, XX] | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX |
| <i>Deep WMH Fazekas score</i> | | | | | | | | | | | | | | |
| | | | | | OLR | XX | | | OLR | XX | | | OLR | XX |
| 1 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 2 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 3 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| Change from baseline | XX | XX [XX, XX] | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX |
| <i>Periventricular and/or Deep WMH Fazekas score</i> | | | | | | | | | | | | | | |
| | | | | | OLR | XX | | | OLR | XX | | | OLR | XX |
| 1 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 2 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | OR/MD/HR (95%CI) | p-value | Cil | No Cil | OR/MD/HR (95%CI) | p-value | ISMN + Cil | None | OR/MD/p-value (95%CI) |
|---------------------------------|----|-------------|-------------|-------------|------------------|---------|-------------|-------------|------------------|---------|-------------|-------------|-----------------------|
| 3 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Change from baseline | XX | XX [XX, XX] | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR XX |
| WMH change from randomisation | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |
| <i>Frontal (%)</i> | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| More | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Less | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| No Change | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| <i>Parietal (%)</i> | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| More | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Less | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| No Change | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| <i>Occipital (%)</i> | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| More | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Less | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| No Change | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| <i>Basal ganglia (%)</i> | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| More | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Less | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| No Change | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| <i>Posterior fossa (%)</i> | | | | | OLR | XX | | | OLR | XX | | | OLR XX |
| More | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Less | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| No Change | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | |
| Old vascular lesions (%) | | | | | | | | | | | | | |
| Old vascular lesions | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |
| Old cortical infarct | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |
| Old striatocapsular infarct | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR XX |

LACI-2 SAP V1.5

06/06/2022

| | N | All | ISMN | No ISMN | OR/MD/HR (95%CI) | p-value | Cil | No Cil | OR/MD/HR (95%CI) | p-value | ISMN + Cil | None | OR/MD/HR (95%CI) | p-value |
|---|----|-------------|-------------|-------------|------------------|---------|-------------|-------------|------------------|---------|-------------|-------------|------------------|---------|
| Old borderzone infarct | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Old lacunar infarct | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| <i>Number of lacunes (%)</i> | | | | | OLR | XX | | | OLR | XX | | | OLR | XX |
| 1 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 2 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 3 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| 4 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| >=5 | XX | XX (X) | XX (X) | XX (X) | | | XX (X) | XX (X) | | | XX (X) | XX (X) | | |
| Change in number of lacunes from baseline | XX | XX [XX, XX] | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX | XX [XX, XX] | XX [XX, XX] | OLR | XX |
| Old brainstem/cerebellar infarcts | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Probable old haemorrhage | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Non-stroke lesions (%) | | | | | | | | | | | | | | |
| Non-stroke lesion | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| <i>Classification of non-stroke (%)</i> | | | | | | | | | | | | | | |
| Cerebral tumour | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Aneurysm | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Vascular malformation | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |
| Other non-stroke classification | XX | XX (X) | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX | XX (X) | XX (X) | BLR | XX |

LACI-2 SAP V1.5

06/06/2022

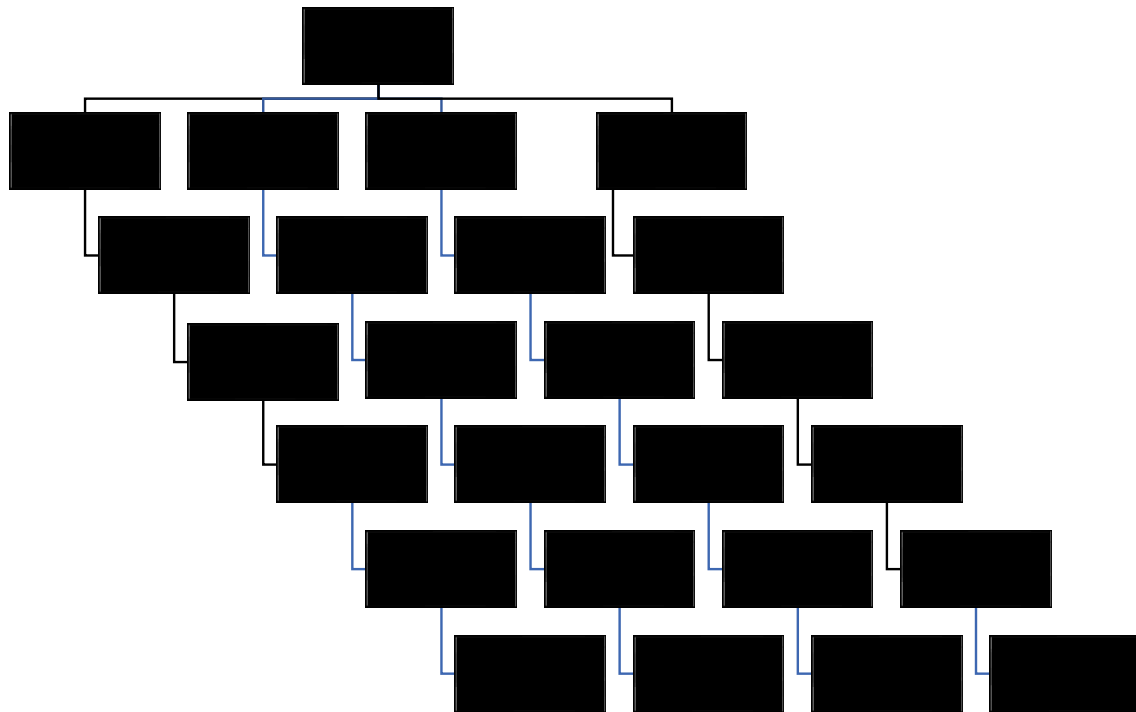
Figures

1. CONSORT flowchart diagram
2. Forest plot of composite outcome (stroke, TIA, MI, cognitive impairment, dependency or death) by clinical and adjudicated imaging subgroups
3. Forest plot of 7-level ordinal cognition/dementia scale by clinical and adjudicated imaging subgroups
4. Forest plot of Wei-Lachin global outcome by clinical and adjudicated imaging subgroups
5. Forest plot of central imaging reads as per list for table 9 of absolute and change in imaging findings
6. Stacked distributions of 7-level ordinal cognition at 12 months
7. Stacked distributions of 4-level ordinal cognition at 12 months
8. Stacked distributions of mRS at 12 months
9. Graph of imaging outcomes at 12 months (based on Table 9) displaying new incident infarct or haemorrhage, change in WMH, microbleeds, atrophy by allocated group.

LACI-2 SAP V1.5

06/06/2022

Figure 1. CONSORT diagram



LACI-2 SAP V1.5

06/06/2022

Figure 2a. Forest plot for isosorbide mononitrate versus none of composite outcome (stroke, TIA, MI, cognitive impairment, dependency or death) by clinical and adjudicated imaging subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | - |
| 180-364 days | - |
| ≥365 days | - |
| Smoking | |
| Never | - |
| Past | - |
| Present | - |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |

LACI-2 SAP V1.5

06/06/2022

| | |
|-----------|---|
| SVD score | |
| 0 | - |
| 1 | - |
| >1 | - |

† Minimisation variable

LACI-2 SAP V1.5

06/06/2022

Figure 2b. Forest plot for cilostazol versus none of composite outcome (stroke, TIA, MI, cognitive impairment, dependency or death) by clinical and adjudicated imaging subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | |
| 180-364 days | |
| ≥365 days | |
| Smoking | |
| Never | |
| Past | |
| Present | |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Minimisation variable

LACI-2 SAP V1.5

06/06/2022

Figure 2c. Forest plot for combined isosorbide mononitrate and cilostazol versus neither of composite outcome (stroke, TIA, MI, cognitive impairment, dependency or death) by clinical and adjudicated imaging subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | - |
| 180-364 days | - |
| ≥365 days | - |
| Smoking | |
| Never | - |
| Past | - |
| Present | - |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Minimisation variable

LACI-2 SAP V1.5

06/06/2022

Figure 3a. Forest plot of 7 level cognition scale for isosorbide mononitrate versus none at 12 months by clinical and adjudicated imaging subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | |
| 180-364 days | |
| ≥365 days | |
| Smoking | |
| Never | |
| Past | |
| Present | |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Adjustment variable

LACI-2 SAP V1.5

06/06/2022

Figure 3b. Forest plot of 7 level cognition scale for cilostazol versus none at 12 months by clinical and adjudicated imaging subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | - |
| 180-364 days | - |
| ≥365 days | - |
| Smoking | |
| Never | - |
| Past | - |
| Present | - |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Adjustment variable

LACI-2 SAP V1.5

06/06/2022

Figure 3c. Forest plot of 7 level cognition scale for combined isosorbide mononitrate and cilostazol versus neither at 12 months by baseline subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | - |
| 180-364 days | - |
| ≥365 days | - |
| Smoking | |
| Never | - |
| Past | - |
| Present | - |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Adjustment variable

LACI-2 SAP V1.5

06/06/2022

Figure 4a. Forest plot of Wei-Lachin global outcome for isosorbide mononitrate versus none by subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | - |
| 180-364 days | - |
| ≥365 days | - |
| Smoking | |
| Never | - |
| Past | - |
| Present | - |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Adjustment variable

LACI-2 SAP V1.5

06/06/2022

Figure 4b. Forest plot of Wei-Lachin global outcome for cilostazol versus none by subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | - |
| 180-364 days | - |
| ≥365 days | - |
| Smoking | |
| Never | - |
| Past | - |
| Present | - |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Adjustment variable

LACI-2 SAP V1.5

06/06/2022

Figure 4c. Forest plot of Wei-Lachin global outcome for combined isosorbide mononitrate and cilostazol versus neither by subgroups. Adjusted

| | Interaction p |
|-------------------------------------|---------------|
| Age † | |
| <60 | - |
| 60-69 | - |
| ≥70 | - |
| Sex † | |
| Female | - |
| Male | - |
| Highest education † | |
| A-level (equivalent) or higher | - |
| O-level/GCSE (equivalent) | - |
| Primary or secondary primary school | - |
| Pre-morbid mRS † | |
| 0 | - |
| 1 | - |
| >1 | - |
| Time stroke-baseline † | |
| <180 days | |
| 180-364 days | |
| ≥365 days | |
| Smoking | |
| Never | |
| Past | |
| Present | |
| Hypertension | |
| No | - |
| Yes | - |
| Diabetes mellitus | |
| No | - |
| Yes | - |
| History of stroke or TIA | |
| No | - |
| Yes | - |
| Systolic BP † | |
| <130 | - |
| 130-159 | - |
| ≥160 | - |
| NIHSS † | |
| 0/1 | - |
| >1 | - |
| Relevant acute infarct on imaging | |
| No | - |
| Yes | - |
| Lacune on imaging | |
| Not visible | - |
| Visible | - |
| WMH or hypoattenuation | |
| Not visible | - |
| Visible | - |
| SVD score | |

LACI-2 SAP V1.5

06/06/2022

| | |
|----|---|
| 0 | - |
| 1 | - |
| >1 | - |

† Adjustment variable

LACI-2 SAP V1.5

06/06/2022

Figure 5. Forest plot of central imaging reads as per list for table 9 of absolute and change in imaging findings

- a) Isosorbide mononitrate versus none
- b) Cilostazol versus none
- c) Combined isosorbide mononitrate and cilostazol versus neither

Figure 6. Stacked distributions of 7-level ordinal cognition at 12 months

- d) Isosorbide mononitrate versus none
- e) Cilostazol versus none
- f) Combined isosorbide mononitrate and cilostazol versus neither

Figure 7. Stacked distributions of 4-level ordinal cognition at 12 months

- a) Isosorbide mononitrate versus none
- b) Cilostazol versus none
- c) Combined isosorbide mononitrate and cilostazol versus neither

Figure 8. Stacked distributions of mRS at 12 months

- a) Isosorbide mononitrate versus none
- b) Cilostazol versus none
- c) Combined isosorbide mononitrate and cilostazol versus neither

Figure 9. Graph of imaging outcomes at 12 months (based on Table 9) displaying new incident infarct or haemorrhage, change in WMH, microbleeds, atrophy by allocated group.

- a) Isosorbide mononitrate versus none
- b) Cilostazol versus none
- c) Combined isosorbide mononitrate and cilostazol versus neither

Signature:

Email: laci-2@ed.ac.uk












LACI-2 SAP v1.5 20220606

Final Audit Report


2022-06-15


| | |
|-----------------|--|
| Created: | 2022-06-08 |
| By: | Sian Irvine (sian.irvine@ed.ac.uk) |
| Status: | Signed |
| Transaction ID: | CBJCHBCAABAahjlv2n-mGfbkbnDio0Cvi-NrpFWzqFO9 |


"LACI-2 SAP v1.5 20220606" History

-  Document created by Sian Irvine (sian.irvine@ed.ac.uk)
2022-06-08 - 12:51:32 PM GMT- IP address: 31.48.48.183
-  Document emailed to Philip Bath (philip.bath@nottingham.ac.uk) for signature
2022-06-08 - 12:53:48 PM GMT
-  Email viewed by Philip Bath (philip.bath@nottingham.ac.uk)
2022-06-09 - 9:01:11 AM GMT- IP address: 92.40.132.99
-  Document e-signed by Philip Bath (philip.bath@nottingham.ac.uk)
Signature Date: 2022-06-09 - 9:02:15 AM GMT - Time Source: server- IP address: 92.40.132.99
-  Document emailed to Joanna Wardlaw (joanna.wardlaw@ed.ac.uk) for signature
2022-06-09 - 9:02:19 AM GMT
-  Email viewed by Joanna Wardlaw (joanna.wardlaw@ed.ac.uk)
2022-06-09 - 11:04:31 AM GMT- IP address: 172.224.227.28
-  Document e-signed by Joanna Wardlaw (joanna.wardlaw@ed.ac.uk)
Signature Date: 2022-06-09 - 1:31:46 PM GMT - Time Source: server- IP address: 212.187.183.33
-  Document emailed to alan montgomery (alan.montgomery@nottingham.ac.uk) for signature
2022-06-09 - 1:31:49 PM GMT
-  Email viewed by alan montgomery (alan.montgomery@nottingham.ac.uk)
2022-06-15 - 7:54:36 AM GMT- IP address: 167.98.250.154
-  Document e-signed by alan montgomery (alan.montgomery@nottingham.ac.uk)
Signature Date: 2022-06-15 - 7:55:08 AM GMT - Time Source: server- IP address: 167.98.250.154
-  Document emailed to laci-2@ed.ac.uk for signature
2022-06-15 - 7:55:11 AM GMT

**Adobe Acrobat Sign**

 Email viewed by laci-2@ed.ac.uk
2022-06-15 - 7:58:40 AM GMT- IP address: 129.215.89.68

 A signed copy was uploaded by Sian Irvine (sian.irvine@ed.ac.uk)
2022-06-15 - 9:26:35 AM GMT

 Agreement completed.
2022-06-15 - 9:26:35 AM GMT

