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

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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

lCerebral 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 bleeding[3] and intensive antihypertensive therapy did not reduce recurrence or prevent cognitive decline[4] 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 cylase-phosphodiesterase-5 and prostacyclin (PGI_2)-cyclic adenylate cylase-phosphodiesterase-3 systems are attractive since they mimic key endogenous vaso-regulators.[2] Both NO and PGI_2 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

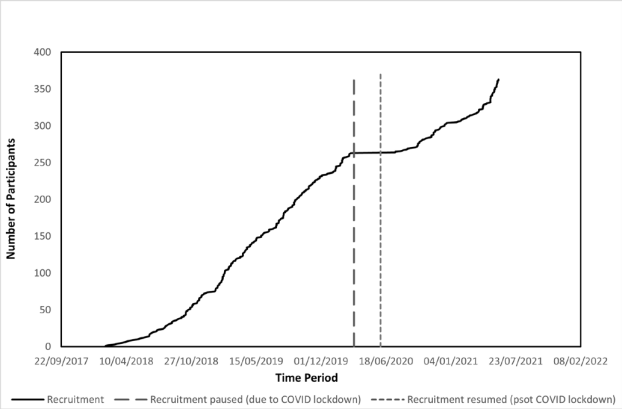

Figure 1 Recruitment by time.

a dipyridamole[7] or sildenafil) to increase and preserve levels of the NO second messenger, cyclic guanylate monophosphate. Although PGI_2 has to be administered intravenously, PDE3 may be inhibited with cilostazol,[8] which preserves levels of the PGI_2 second messenger, cyclic adenylate monophosphate; cilostazol has showed promise in secondary prevention trials in ischaemic stroke, which included large proportions of patients with lacunar stroke subtype[8]; 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] 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 stroke[23]; additionally, these drugs appeared to reduce arterial stiffness without effects on platelet function[22] 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

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)
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)

Continued

Table 1 Continued

Variable	N	Participants	cSVD	Score*
		All	None/mild	Moderate to severe
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.

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

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

Variable	N	Participants All	cSVD Score* None/mild	Moderate to evere	P value
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)	

Continued

Table 2 Continued

Variable	N	Participants All	cSVD None/mild	Score* Moderate to evere	P value
ECG (%)					0.93
Sinus	360	347 (96.4)	94 (95.9)	253 (96.6)	
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.

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 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 read (3%), the remaining 97% having either a recent

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	All	SVD Low	Score Moderate-severe	P value
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
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.

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 a online supplemental file. If reasonable drug adherence and safety are confirmed, then a phase III trial will be

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 Score		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.

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

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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.

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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.

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Correction: *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)*

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 Vasc Neurol* 2022;svn-2022-001816. doi: 10.1136/svn-2022-001816

The article was erroneously published without the full title as 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). This has been amended to Cilostazol and isosorbide mononitrate for the prevention of progression of cerebral small vessel disease: baseline data and statistical analysis plan for the Lacunar Intervention Trial-2 (LACI-2) (ISRCTN14911850). Also, there are LACI 2 Investigators added along with author names in title page. The details of the investigators are added as a supplemental material in the article.

Stroke Vasc Neurol 2023;**8**:e001816corr1. doi:10.1136/svn-2022-001816corr1

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	Philip Bath Philip Bath (Jun 9, 2022 10:02 GMT+1)	Jun 9, 2022
6b Senior statistician	Alan Montgomery	A. Montgomery	Jun 15, 2022
6c Chief Investigator:	Joanna Wardlaw	Joanna Wardlaw	Jun 9, 2022

SECTION 2. INTRODUCTION

7 Background and rationale

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 ≤/>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] our [11-13] and other [14] 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

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]).

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

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).

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]

- SVD score for CT = WML, lacunes; for MRI includes WMH, lacunes, PVS and microbleeds [15]

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:

- 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 test [18-21] 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-V [22] 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

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 No evidence of functional impairment (mRS <2 OR no change in mRS if pre-stroke mRS >1)
	Multi-domain Scores are reduced by > 1 point in more than one cognitive domain of T-MoCA	
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) OR 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
	Moderate cognitive impairments (T-MoCA 10-14 OR TICS-m 12-16) **AND** **Moderate dysfunction** (mRS 3 or 4)	
	Severe cognitive impairments (T-MoCA <10 OR TICS-m <12) **AND** **Severe dysfunction**	

	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

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.

ABREVIATIONS

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

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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)

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)	
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)

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)		
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

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		XX (X)
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)

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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.

Number	ISMN	No ISMN	Difference (p)	Cilostazol	No cilostazol	Difference (p)	ISMN + Cil	Neither	Difference (p)
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)	

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			OLR			OLR			OLR
Normal	XX (X)	XX (X)		XX (X)	XX (X)		XX (X)	XX (X)	
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

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).

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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.

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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										
Scan type(%)										
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 (%)										

	N	All	ISMN	No ISMN	CiI	No CiI	ISMN + CiI	ISMN only	CiI only	None
Index small subcortical (i.e. acute lacunar) infarct	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)
No. microhaemorrhages (%)										
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)
Type of microhaemorrhages (%)										

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	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)
Siderosis location										
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)
Anterior white matter lucency										
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)
Posterior white matter lucency										
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)
Anterior and/or Posterior white matter lucency										

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	N	All	ISMN	No ISMN	CiI	No CiI	ISMN + CiI	ISMN only	CiI 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)
Periventricular WMH Fazekas score										
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)
Deep WMH Fazekas score										
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)
Periventricular and/or Deep WMH Fazekas score										
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)
Basal ganglia rating, worse side										
<=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)
Centrum semiovale rating, worse side										
<=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 (%)										

	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)
Number of lacunes (%)										
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)
Classification of non-stroke (%)										
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)

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)	-

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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.

	All			Fatal		
	ISMN	**No ISMN**	**Difference (p)**	**ISMN**	**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

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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

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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.

	All			Fatal		
Number	ISMN /Cil	No ISNM /Cil	Difference (p)	ISMN /Cil	No ISNM /Cil	Difference (p)
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

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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

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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 (%)														

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	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
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
No. microhaemorrhages (%)					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)		

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	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
Anterior white matter lucency														
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
Posterior white matter lucency														
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
Anterior and/or Posterior white matter lucency														
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
Periventricular WMH Fazekas score					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
Deep WMH Fazekas score					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
Periventricular and/or Deep WMH Fazekas score					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)		

	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
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
Frontal (%)					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)		
Parietal (%)					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)		
Occipital (%)					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)		
Basal ganglia (%)					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)		
Posterior fossa (%)					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

	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
Number of lacunes (%)					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
Classification of non-stroke (%)														
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

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.

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Figure 1. CONSORT diagram

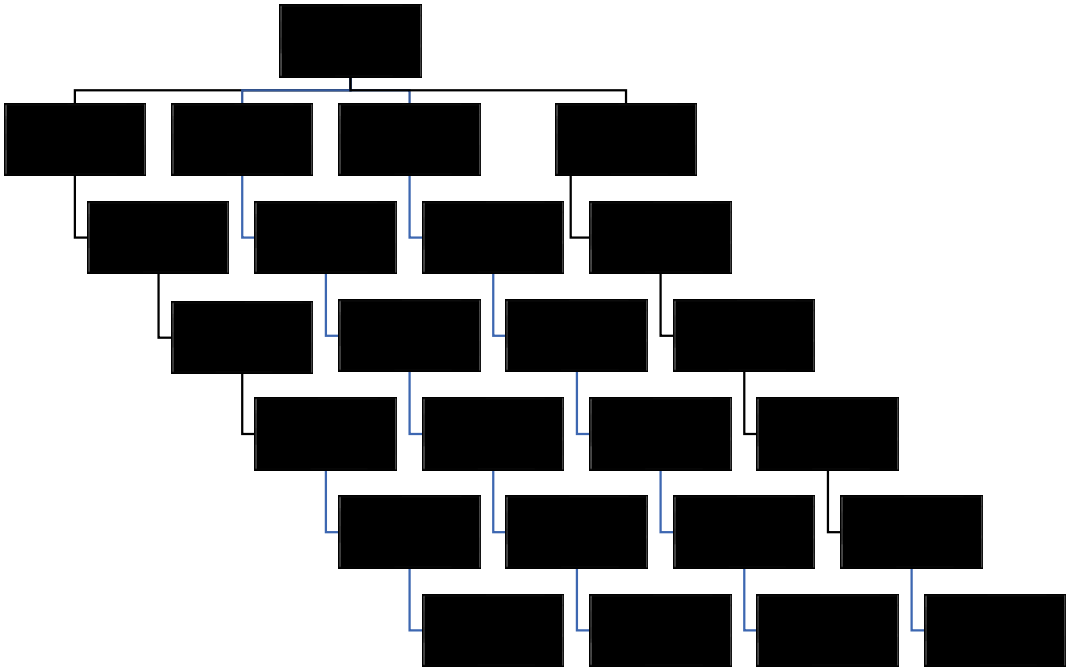

Figure 2a. Forest plot for isosorbide mononitrate versus none of composite outcome (stroke, TIA, MI, cognitive impairment, dependency or death) by clinical and adjudicated imaging subgroups. Adjusted

	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	-

SVD score	
0	-
1	-
>1	-

† Minimisation variable

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	

0	-
1	-
>1	-

† Minimisation variable

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	

0	-
1	-
>1	-

† Minimisation variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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

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LACI-2 SAP v1.5 20220606

Final Audit Report 2022-06-15

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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	Philip Bath Philip Bath (Jun 9, 2022 10:02 GMT+1)	Jun 9, 2022
6b Senior statistician	Alan Montgomery	A. Montgomery	Jun 15, 2022
6c Chief Investigator:	Joanna Wardlaw	Joanna Wardlaw	Jun 9, 2022

SECTION 2. INTRODUCTION

7 Background and rationale

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 ≤/>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] our [11-13] and other [14] 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

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]).

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

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).

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]

- SVD score for CT = WML, lacunes; for MRI includes WMH, lacunes, PVS and microbleeds [15]

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:

- 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 test [18-21] 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-V [22] 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

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 No evidence of functional impairment (mRS <2 OR no change in mRS if pre-stroke mRS >1)
	Multi-domain Scores are reduced by > 1 point in more than one cognitive domain of T-MoCA	
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) OR 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
	Moderate cognitive impairments (T-MoCA 10-14 OR TICS-m 12-16) **AND** **Moderate dysfunction** (mRS 3 or 4)	
	Severe cognitive impairments (T-MoCA <10 OR TICS-m <12) **AND** **Severe dysfunction**	

	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

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.

ABREVIATIONS

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

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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)

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)	
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)

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)		
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

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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		XX (X)
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)

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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.

Number	ISMN	No ISMN	Difference (p)	Cilostazol	No cilostazol	Difference (p)	ISMN + Cil	Neither	Difference (p)
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)	

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			OLR			OLR			OLR
Normal	XX (X)	XX (X)		XX (X)	XX (X)		XX (X)	XX (X)	
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

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).

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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.

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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										
Scan type(%)										
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 (%)										

	N	All	ISMN	No ISMN	CiI	No CiI	ISMN + CiI	ISMN only	CiI only	None
Index small subcortical (i.e. acute lacunar) infarct	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)
No. microhaemorrhages (%)										
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)
Type of microhaemorrhages (%)										

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	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)
Siderosis location										
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)
Anterior white matter lucency										
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)
Posterior white matter lucency										
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)
Anterior and/or Posterior white matter lucency										

	N	All	ISMN	No ISMN	CiI	No CiI	ISMN + CiI	ISMN only	CiI 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)
Periventricular WMH Fazekas score										
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)
Deep WMH Fazekas score										
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)
Periventricular and/or Deep WMH Fazekas score										
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)
Basal ganglia rating, worse side										
<=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)
Centrum semiovale rating, worse side										
<=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 (%)										

	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)
Number of lacunes (%)										
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)
Classification of non-stroke (%)										
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)

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)	-

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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.

	All			Fatal		
	ISMN	**No ISMN**	**Difference (p)**	**ISMN**	**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

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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

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.

	All			Fatal		
Number	ISMN /Cil	No ISNM /Cil	Difference (p)	ISMN /Cil	No ISNM /Cil	Difference (p)
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

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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

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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 (%)														

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	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
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
No. microhaemorrhages (%)					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)		

	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
Anterior white matter lucency														
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
Posterior white matter lucency														
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
Anterior and/or Posterior white matter lucency														
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
Periventricular WMH Fazekas score					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
Deep WMH Fazekas score					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
Periventricular and/or Deep WMH Fazekas score					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)		

	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
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
Frontal (%)					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)		
Parietal (%)					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)		
Occipital (%)					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)		
Basal ganglia (%)					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)		
Posterior fossa (%)					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

	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
Number of lacunes (%)					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
Classification of non-stroke (%)														
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

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.

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Figure 1. CONSORT diagram

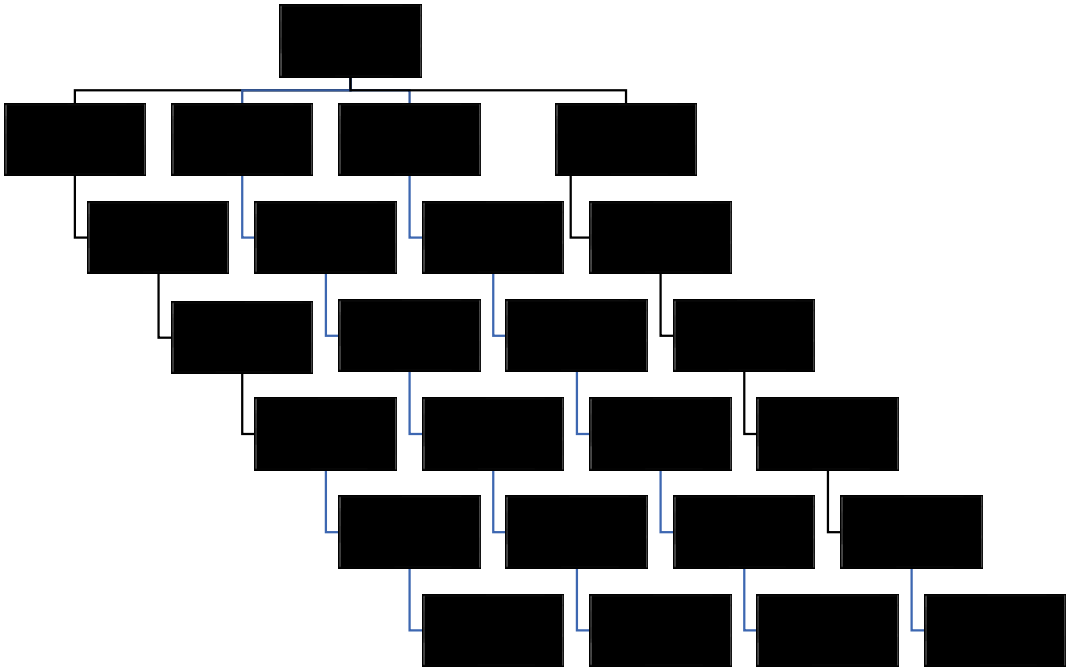

Figure 2a. Forest plot for isosorbide mononitrate versus none of composite outcome (stroke, TIA, MI, cognitive impairment, dependency or death) by clinical and adjudicated imaging subgroups. Adjusted

	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	-

SVD score	
0	-
1	-
>1	-

† Minimisation variable

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	

0	-
1	-
>1	-

† Minimisation variable

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	

0	-
1	-
>1	-

† Minimisation variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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	

0	-
1	-
>1	-

† Adjustment variable

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

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LACI 2 Investigator Group

Chief Investigator: Professor Joanna M Wardlaw

Grant Co-Applicants/Project management group: Philip Bath (Co-CI), Vera Cvoro, Fergus Doubal, Timothy England, Ahamad Hassan, Alan Montgomery, Nikki Sprigg, Joanna Wardlaw, David Werring.

Trial steering committee:

Chairperson: John Bamford

Independent Scientific Members: John O'Brien, Christine Roffe

Independent Participant Representative: Euan Haig,

Non-Independent Members**:** Shannon Amoils, Philip Bath, Julia Boyd, Vera Cvoro, Fergus Doubal, Timothy England, Ahamad Hassan, Anna Heye, Iris Mhlanga, Alan Montgomery, Katherine Oatey, Fiach O'Mahony, Nikki Sprigg Joanna Wardlaw, David Werring, Lisa Woodhouse.

Observers**:** Jason Appleton, Gordon Blair, Kaye Ferguson, Anna Foster, Sian Irvine, Zhe Kang Law, Eleni Sakka, Carol Williams,

Data monitoring committee:

Chairperson: Colin Baigent

Independent Members: Gary Ford, Jonathan Emberson, Alison Murray (inception – 2021), A Ross Naylor (2021 - end)

Independent Blinded Event Adjudication: Fergus Doubal, Nikki Sprigg, Kailash Krishnan

Edinburgh Trial Staff

Clinical Trials Unit and Centre for Clinical Brain Sciences related staff: Julia Boyd, Christine Campbell, Anna Heye, Kaye Ferguson, Anna Foster, Sian Irvine, Katherine Lewis, Lynne McGillivray, Katherine Oatey, Nicole Porter, Pamela Sinclair, Joyce Thomson. Debbie Alexander, Susan Begg, Kate Covil, Judy Coyle, Debbie Hamilton, Guen Innes, Helen Watters, Carol Williams.

Image Data Management: Eleni Sakka, Jeb Palmer, David Buchanan.

Nottingham Trial Staff

Stroke Trials Unit and related staff: Cydney Bruce, Sharon Ellender, Robert Gray, Diane Havard, Lee Haywood, Olivier Matias, Patricia Robinson, Cameron Skinner.

Programming eCRF and data management: Richard Dooley, Athfi Rijal Mufied, Lee Hayward.

Statisticians: Lisa Woodhouse, Iris Mhlanga

DMC - provide blinded statistical report with key: Cydney Bruce, Wei Tan

Participating Sites:

Edinburgh, Royal Infirmary, C001: Fergus Doubal (PI), Carmen Arteaga Reyes, Gayle Barclay, Gordon Blair, Brittany Bovenzi, Ruaridh Buchan, Seona Burgess, Una Clancy, Michelle Coakley, Angie Crawford, Sean Denham, Nicholas Fethers, Iona Hamilton, Charlotte Jardine, Lucy Kessler, Allan MacRaild, Donna McIntyre, Emma Moatt, Rachel Penman, Rustam Al-Shahi Salman, Elaine Sandeman, Jennifer Tait, Pat Taylor, Jessica Teasdale, William Whiteley

Nottingham, University Hospitals, C002: Kailash Krishnan (PI), Jason Appleton, Philip Bath, Amanda Buck, Lucy Fleming, Sheila Hodgson, Ashah Kumar, Zhe Kang Law, Carla Richardson, Rosie Roberts, Nikola Sprigg, Gemma Squires, Gwen Wilkes.

Kirkcaldy, Victoria Hospital, C004: Vera Cvoro (PI), Mandy Couser,

Glasgow, Queen Elizabeth Hospital, C005: Jesse Dawson (PI), Sandee Beattie, Alan Cameron, Ozlem Dincarslan, Laura Dymock, Helen Hart, Tracey Hopkins, Pamela MacKenzie, Belinda Manak, Lesley McDonald, Evonne McLennan, Karen Montgomery, Azmil Abdul-Rahim, Colin Rodden, Jennifer Tait, Linda Taylor, Nicola Tynan, Rosie Woodward.

Bradford, Royal Infirmary, C006: Chris Patterson (PI), Eman Abdussami, Ruth Bellfield, Numan Khan, Stuart Maguire, Outi Quinn, Kelvin Stewart.

Aberdeen Royal Infirmary, C007: German Guzman Gutierrez (PI), Jacqueline Furnace, Janice Irvine, Mary J MacLeod, Vicky Taylor, Sandra Williams.

Leeds General Infirmary, C008: Ahamed Hassan (PI), Nathan Douglas, Ana Garcia, Luis Idrovo, Linetty Makawa, Vasileios Papavasileiou, Marc Randall, Emelda Veraque, Dean Waugh.

Derby, Royal Derby Hospital, C009: Timothy England (PI), Wendy Abbott, Sathon Boonyapragon, Jessica Beavan, Liz Bedford, Richard Donnelly, Michelle Fanuncio, Marie Goldsworthy, Margaret Harper, Amanda Hedstrom, Katie Large, Peter Mason, Lisa Mayles, Harry McNaughton, Beverley Rushton, James Scott, Hege Strand, Kashmira Subramanian Shenila Zaya.

Inverness Raigmore Hospital, C010: Stephen Makin (PI), Fiona Barrett, Clare Bradley, Jim Finlayson, Ashish Macaden, Joanna Matheson, Debbie McDonald, Mary Mckenzie, Donna Patience, Lesley Sanders, Adam Scotson, Zoe Urquhart.

London, St George's Hospital, C011: Usman Khan (PI), Rebecca Williams

London, Kings College Hospital, C012: Laszlo Sztriha (PI), Thomas Booth (PI), John Aeron-Thomas, Myriam Aissa, Sandeep Ankolekar, Sara Bik, Ajay Bhalla, , Frederick Boyle, Stuart Chandler, Staci Conway, Mena Farag, Maria Garcia-Pardo, Chong Ho, Fiona Humphries, Madawi Ismail, Agnieszka Kieliszkowska, Yee Mah, Esther Makanju, Dulka Manawadu, Georgina Meredith, Erika Manolo, Gaynor Notcheva, Elliott Smith, James Teo, Evangeline Theochari, Maria Consuelo Tibajia.

Essex, Broomfield Hospital, C013: amanathan Kirthivasan (PI), Abdulraza Alsowmely, Emma Cannon, Caroline Fox, Victoria Mead, Iman Mohamed.

Stockton-on-Tees, University Hospital of North Tees, C014: Anwar Ijaz (PI), Arunkumar Annamalai, Vicky Collins, Helen Dunn, Sarah Pitcairn, Alex Ramshaw, Lorna Shepherd, Elaine Siddle, Bill Wetherill

Sheffield, Royal Hallamshire Hospital, C015: Kirsty Harkness (PI), Jon Gardner, Jo Howe, Christine Kamara, Emma Richards, Madalina Roman, Mary Sikaonga

Sandwell, General Hospital, West Bromwich, C016: Sevasti Ispoglou (PI), Steven Billingham, Anne Hayes, Lindsay Hough, Steven Shanu

Winchester, Royal Hampshire County Hospital, C017: Nigel Smyth (PI), John Duffy, Charlotte Eglinton, Lucy Engin, Carolyn Fitton, Isi Ikhurionan, Lauriane Kerwood, Lucy Sykes, Ela Tone

London, University College, C018: David Werring (PI), Amy Ashton, Azra Banaras, Nina Bason, Jonathan Best, Cyrille Mae Cahoy, Kevin Cregg, Kirsty Dimond, Scheherazade Feerick, Nina Francia, Simon Heller, Fiona Humphries, Howell Jones, Arnab Mandal, Marilena Marinescu, Sandra Mascarenhas, Talal Mayhani, Sabaa Obarey, Temi Olusi, Nikita Parmar, Richard Perry, Graziella Quattrocchi, Anna Robinson, Sadia Saber, Yezen Sammaraiee, Nayema Tahmin, Kristian Warnes, Caroline Watchurst, Annick Williams.

Harrow, Northwick Park Hospital, C019: Aravinth Sivagnanaratnam (PI), David Cohen (PI), Gbadebo Adewetan, Rachel Baldwin Cleland, Robert Ballantine, Lara Barcella, Rajaram Bathula, Daniel Brooks, Swati Chhabra, Bindiya Kerai, Matilda Lang, Mushiya Mpelembue, Jasmin Patel, Phillip Regelous, Sreena Sreedevi Raj, Nicholas Winterkorn, Priya Yesupatham.

Luton, Luton and Dunstable NHSFT University Hospital, C020: Lakshmanan Sekaran (PI), Lankanatha Alwis, Jane Angus, Asaipillai Asokanathan, Caroline Fornolles, Frances Justin, Duke Phiri, Sakthiviel Sethuraman, Margaret Louise Tate.

Doncaster Royal Infirmary, C021: Dinesh Chadha (PI), Fiona Dunning, Mark Fairweather, Rebecca Pugh, Jeannette Stretton, Deborah Walstow, Sayed Zafar

Wolverhampton, New Cross Hospital, C022: Nasar Ahmad (PI), Jumoke Adeyemi, Ann Bentley, Emily Carter, Rachel Evans, Kenneth Fotherby, Rachael Jones, Kulbinder Kauldhar, Samuel Nyabam, Victoria Shakespeare, Angela Stevens, Chris Wharton, Angela Wilberry, Jiao Yunzheng.

Halifax, Calderdale Hospital, C023: Pratap Rana (PI), Megan Collins, Jill Greig, Mohammad Irfan Azam, Manohar Kini, Adam Mawer, Tonicha Nortcliffe, Ridha Ramiz, Matthew Robinson, Ryan Shaw, Kathryn Smith, Hayley Webster.

Taunton, Musgrove Park Hospital, C025: Malik Hussain (PI), Richard Burgess, Kimberley Gillman, Dumin Karunatilake, Tamlyn Russell, Tania Wainwright, Alison Whitcher, Esther Zebracki

Southampton General Hospital, C026: Nic Weir (PI), Michelle Beveridge, Alex Blades, Sue Evans, Efe Evbuomwan, Tomas Hannam-Penfold, Jake Harvey, Sneha Jethwa, Richard Marigold, Mariya Shaji, Simon Smith.

London, Homerton University Hospital, C027: Thomas Harrison (PI), Ayesha Begum, Hannah Bouattia, Rebecca Brady, Luisa Cabrero, Kiran Dahele, Catherine Holbrook, Mudassar Hussain, Derya Ovayolu, Nideya Sharif, Penelope Talelli, Helen White.

Exeter - Royal Devon & Exeter Hospital, C028: Salim Elyas (PI), Angie Bowring, Alina Govier, Martin James, Samantha Keenan, Jessica Kubie, Paul Mudd, Jane Sword.