

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

EudraCT number	2016-002277-35
Trial protocol	GB
Global end of trial date	12 September 2022

Results information

Result version number	v1 (current)
This version publication date	16 September 2023
First version publication date	16 September 2023

Trial information**Trial identification**

Sponsor protocol code	AC16093
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Additional study identifiers

ISRCTN number	ISRCTN14911850
ClinicalTrials.gov id (NCT number)	NCT03451591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACCORD
Sponsor organisation address	The Queen's Medical Research Institute 47 Little France Crescent Edinburgh, , Edinburgh, United Kingdom, EH16 4TJ
Public contact	Fiach O'Mahony, University of Edinburgh, +44 01312429418, Fiach.omahony@ed.ac.uk
Scientific contact	Fiach O'Mahony, University of Edinburgh, +44 01312429418, Fiach.omahony@ed.ac.uk
Sponsor organisation name	ACCORD
Sponsor organisation address	The Queen's Medical Research Institute 47 Little France Crescent , Edinburgh , United Kingdom, EH16 4TJ
Public contact	Heather Charles, NHS Lothian/University of Edinburgh, +44 01312423359, heathercharles@nhslothian.scot.nhs.uk
Scientific contact	Heather Charles, NHS Lothian/University of Edinburgh, +44 01312423359, heathercharles@nhslothian.scot.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2022
Global end of trial reached?	Yes
Global end of trial date	12 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The inclusion and exclusion criteria were put in place to ensure only suitable participants entered the study.

Doses were escalated until participants are on their full dose by 1 month. If a patient encounters intolerable side effects at full dose, then they will be able to remain on the highest dose regime that they can tolerate and this dose will be recorded.

Background therapy:

None

Evidence for comparator:

There is no proven treatment for cerebral small vessel disease: conventional antiplatelet drugs may be ineffective or even hazardous, whilst antihypertensive treatment and statins may not have an effect. The disease mechanism is poorly understood but endothelial dysfunction, blood-brain barrier failure and vessel stiffness appear to contribute to the pathogenesis. Promising data available for licensed drugs with relevant modes of action, cilostazol (>6000 stroke patients in the Asia Pacific Region) and isosorbide mononitrate (ISMN, widely used in cardiac disease) support their testing in cerebral small vessel disease.

Actual start date of recruitment	08 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 363
Worldwide total number of subjects	363
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	186
From 65 to 84 years	173
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Between 05/02/2018 and 31/05/2022, LACI-2 recruited 363/400 patients at 26 UK centres.

Pre-assignment

Screening details:

Following consent, the research doctor will confirm that the patient is eligible to participate in the trial as per the inclusion/exclusion criteria. This will be documented in the eCRF and in the patients medical notes.

Period 1

Period 1 title	Baseline to Follow up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor ^[1]

Blinding implementation details:

Structured symptom questionnaires, ascertainment of clinical outcomes and MRI analysis will be collected by individuals blinded to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cilostazol

Arm description:

Cilostazol, generic, as 50mg or 100mg tablets.

Arm type	Experimental
Investigational medicinal product name	Cilostazol
Investigational medicinal product code	B01A C
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cilostazol, generic, as 50mg or 100mg tablets.

Investigational medicinal product name	Isosorbide Mononitrate
Investigational medicinal product code	C01DA14
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Isosorbide mononitrate slow release, generic, for example as 25mg XL or 50mg XL tablets to the suggested target dose of 40-60mg daily.

Isosorbide mononitrate, generic, as 20mg tablets to the suggested target dose of 40-60mg daily.

Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release preparations may be used, but the dose should be split half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in 20mg tablets in which case the 20mg should be substituted for the 25mg dose. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the treatment pack.

Arm title	Isosorbide Mononitrate
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Arm description:

Isosorbide mononitrate slow release, generic, for example as 25mg XL or 50mg XL tablets to the suggested target dose of 40-60mg daily.

Isosorbide mononitrate, generic, as 20mg tablets to the suggested target dose of 40-60mg daily. Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release preparations may be used, but the dose should be split half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in 20mg tablets in which case the 20mg should be substituted for the 25mg dose. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the treatment pack.

Arm type	Active comparator
Investigational medicinal product name	Isosorbide Mononitrate
Investigational medicinal product code	C01DA14
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Isosorbide mononitrate slow release, generic, for example as 25mg XL or 50mg XL tablets to the suggested target dose of 40-60mg daily.

Isosorbide mononitrate, generic, as 20mg tablets to the suggested target dose of 40-60mg daily. Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release preparations may be used, but the dose should be split half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in 20mg tablets in which case the 20mg should be substituted for the 25mg dose. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the treatment pack.

Arm title	Cilostazol + Isosorbide mononitrate
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Arm description:

Both Cilostazol and ISMN

Arm type	Experimental
Investigational medicinal product name	Cilostazol
Investigational medicinal product code	B01A C
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cilostazol, generic, as 50mg or 100mg tablets.

Investigational medicinal product name	Isosorbide Mononitrate
Investigational medicinal product code	C01DA14
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Isosorbide mononitrate slow release, generic, for example as 25mg XL or 50mg XL tablets to the suggested target dose of 40-60mg daily.

Isosorbide mononitrate, generic, as 20mg tablets to the suggested target dose of 40-60mg daily. Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release preparations may be used, but the dose should be split half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in 20mg tablets in which case the 20mg should be substituted for the 25mg dose. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the treatment pack.

Arm title	No IMP
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Arm description: -

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Structured symptom questionnaires, ascertainment of clinical outcomes and MRI analysis will be collected by individuals blinded to treatment allocation so there is an element of blinding to the study.

Number of subjects in period 1	Cilostazol	Isosorbide Mononitrate	Cilostazol + Isosorbide mononitrate
	Started	91	90
Completed	70	70	81
Not completed	21	20	10
Consent withdrawn by subject	7	7	3
Patient refused	7	-	-
Lost to follow-up	7	8	5
Refused	-	5	2

Number of subjects in period 1	No IMP
Started	91
Completed	87
Not completed	4
Consent withdrawn by subject	1
Patient refused	-
Lost to follow-up	3
Refused	-

Baseline characteristics

Reporting groups

Reporting group title	Cilostazol
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Reporting group description:

Cilostazol, generic, as 50mg or 100mg tablets.

Reporting group title	Isosorbide Mononitrate
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Reporting group description:

Isosorbide mononitrate slow release, generic, for example as 25mg XL or 50mg XL tablets to the suggested target dose of 40-60mg daily.

Isosorbide mononitrate, generic, as 20mg tablets to the suggested target dose of 40-60mg daily.

Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release

preparations may be used, but the dose should be split half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in

20mg tablets in which case the 20mg should be substituted for the 25mg dose. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the treatment pack.

Reporting group title	Cilostazol + Isosorbide mononitrate
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Reporting group description:

Both Cilostazol and ISMN

Reporting group title	No IMP
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Reporting group description: -

Reporting group values	Cilostazol	Isosorbide Mononitrate	Cilostazol + Isosorbide mononitrate
Number of subjects	91	90	91
Age categorical Units: Subjects			

Age continuous Units: years median standard deviation	64 ± 73	65 ± 72	63 ± 72
Gender categorical Units: Subjects			
Female	28	27	27
Male	63	63	64
Stroke onset to randomisation ≤ v > 100 days Units: Subjects			
Stroke onset to randomisation ≤100 days	53	54	46
Stroke onset to randomisation > 100 days	38	36	45
Highest Education Level Units: Subjects			
Postgraduate	6	5	10
Undergraduate	9	8	9
A-Level or Equivalent	14	8	14
O-Level/GCSE or Equivalent	30	34	27
Secondary School	32	34	31

Primary School	0	1	0
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Stroke onset to randomisation, days*			
Units: Days			
arithmetic mean	75	74.5	100
standard deviation	± 238.0	± 251.0	± 252.0
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	145.2	145	145.1
standard deviation	± 20.6	± 18.1	± 19.3

Reporting group values	No IMP	Total	
Number of subjects	91	363	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
median	64		
standard deviation	± 74	-	
Gender categorical			
Units: Subjects			
Female	30	112	
Male	61	251	
Stroke onset to randomisation ≤ v > 100 days			
Units: Subjects			
Stroke onset to randomisation ≤100 days	53	206	
Stroke onset to randomisation > 100 days	38	157	
Highest Education Level			
Units: Subjects			
Postgraduate	6	27	
Undergraduate	11	37	
A-Level or Equivalent	18	54	
O-Level/GCSE or Equivalent	23	114	
Secondary School	32	129	
Primary School	1	2	
Stroke onset to randomisation, days*			
Units: Days			
arithmetic mean	77		
standard deviation	± 256.0	-	
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	142.7		
standard deviation	± 20.1	-	

End points

End points reporting groups

Reporting group title	Cilostazol
Reporting group description:	Cilostazol, generic, as 50mg or 100mg tablets.
Reporting group title	Isosorbide Mononitrate
Reporting group description:	Isosorbide mononitrate slow release, generic, for example as 25mg XL or 50mg XL tablets to the suggested target dose of 40-60mg daily. Isosorbide mononitrate, generic, as 20mg tablets to the suggested target dose of 40-60mg daily. Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release preparations may be used, but the dose should be split half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in 20mg tablets in which case the 20mg should be substituted for the 25mg dose. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the treatment pack.
Reporting group title	Cilostazol + Isosorbide mononitrate
Reporting group description:	Both Cilostazol and ISMN
Reporting group title	No IMP
Reporting group description:	-

Primary: Feasibility of Trial

End point title	Feasibility of Trial ^[1]
End point description:	Feasibility of Phase III trial, i.e. that eligible patients can be identified correctly, in sufficient numbers, enrolled and >95% retained in follow-up at one year, to achieve feasibility target sample size recruitment and randomisation of 400 patients in 24 months in the UK.
End point type	Primary
End point timeframe:	12 month

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary endpoint is a count of participants recruited. No special analysis was completed for this endpoint and no p-values were presented.

End point values	Cilostazol	Isosorbide Mononitrate	Cilostazol + Isosorbide mononitrate	No IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	90	91	91
Units: 363				
Completed 12 month FU	70	70	81	87
Withdrawn, Refused, Lost to FU	21	20	10	4

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Dose Specific Trial Medication Tolerability

End point title	Rate of Dose Specific Trial Medication Tolerability
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End point description:

It is estimated that in this trial 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).

Count of participants with adherence to medication at half dose or more at 12 months.

End point type	Secondary
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End point timeframe:

12 months

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment emergent adverse effects [safety]

End point title	Incidence of treatment emergent adverse effects [safety]
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End point description:

Safety - symptoms of systemic or intracranial bleeding, recurrent cerebral and systemic vascular events, and vascular and non-vascular causes of death will be collected. It is estimated that in this trial the absolute risk of death, including fatal haemorrhage, will not differ significantly (ie fall outside the upper 95% CI) from 2% per year on trial drugs versus no trial drugs, when given in addition to guideline drugs; and will not increase bleeding or ischaemic SVD lesions significantly (at the $p < 0.01$ level) on MRI.

End point type	Secondary
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End point timeframe:

12 months

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment efficacy - rate of individual participant events (stroke, TIA, myocardial ischaemia, cognitive impairment and dementia)

End point title	Treatment efficacy - rate of individual participant events (stroke, TIA, myocardial ischaemia, cognitive impairment and dementia)
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End point description:

It is estimated that in this trial the combined rate of recurrent stroke, MI, death, cognitive impairment and dependency will be 40-50% at one year after enrolment in order to detect modest but clinically-important reductions in poor outcomes.

Clinical, functional, QoL and global outcomes at 12 months- Stroke/TIA, MI, Cognitive impairment, Dependency, Death. Data are number (%), or mean (standard deviation).

End point type	Secondary
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End point timeframe:

12 months

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

From randomisation to 12 months

Adverse event reporting additional description:

None

Assessment type	Systematic
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Dictionary used

Dictionary name	Uni of Notts Stroke
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Dictionary version	1.4.8
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Reporting groups

Reporting group title	Cilostazol
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Reporting group description:

Cilostazol, generic, as 50mg or 100mg tablets.

Reporting group title	Isosorbide Mononitrate
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Reporting group description:

Isosorbide mononitrate slow release, generic, for example as 25mg XL or 50mg XL tablets to the suggested target dose of 40-60mg daily.

Isosorbide mononitrate, generic, as 20mg tablets to the suggested target dose of 40-60mg daily.

Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release

preparations may be used, but the dose should be split half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in

20mg tablets in which case the 20mg should be substituted for the 25mg dose. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the treatment pack.

Reporting group title	Cilostazol + Isosorbide mononitrate
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Reporting group description:

Both Cilostazol and ISMN

Reporting group title	No IMP
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Only SAEs were collected for this study as per protocol

Serious adverse events	Cilostazol	Isosorbide Mononitrate	Cilostazol + Isosorbide mononitrate
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 182 (15.93%)	21 / 181 (11.60%)	15 / 91 (16.48%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour/Malignancy			
subjects affected / exposed	4 / 182 (2.20%)	1 / 181 (0.55%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			

Cardiovascular			
subjects affected / exposed	7 / 182 (3.85%)	5 / 181 (2.76%)	4 / 91 (4.40%)
occurrences causally related to treatment / all	2 / 7	2 / 5	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Nervous System			
subjects affected / exposed	7 / 182 (3.85%)	2 / 181 (1.10%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haematological			
subjects affected / exposed	0 / 182 (0.00%)	1 / 181 (0.55%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Other			
subjects affected / exposed	6 / 182 (3.30%)	5 / 181 (2.76%)	3 / 91 (3.30%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	8 / 182 (4.40%)	7 / 181 (3.87%)	5 / 91 (5.49%)
occurrences causally related to treatment / all	0 / 8	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	2 / 182 (1.10%)	1 / 181 (0.55%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Genitourinary			
subjects affected / exposed	4 / 182 (2.20%)	1 / 181 (0.55%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal			
subjects affected / exposed	1 / 182 (0.55%)	1 / 181 (0.55%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection/Sepsis			
subjects affected / exposed	6 / 182 (3.30%)	5 / 181 (2.76%)	2 / 91 (2.20%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events	No IMP		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 91 (13.19%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour/Malignancy			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiovascular			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous System			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haematological			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions Other subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 91 (4.40%) 1 / 4 0 / 0		
Gastrointestinal disorders Gastrointestinal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 91 (1.10%) 0 / 1 0 / 0		
Respiratory, thoracic and mediastinal disorders Respiratory subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 91 (1.10%) 0 / 1 0 / 1		
Renal and urinary disorders Genitourinary subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 91 (1.10%) 0 / 1 0 / 0		
Musculoskeletal and connective tissue disorders Musculoskeletal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 91 (0.00%) 0 / 0 0 / 0		
Infections and infestations Infection/Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 91 (1.10%) 0 / 1 0 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cilostazol	Isosorbide Mononitrate	Cilostazol + Isosorbide mononitrate
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 182 (0.00%)	0 / 181 (0.00%)	0 / 91 (0.00%)

Non-serious adverse events	No IMP		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 91 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 December 2017	Substantial Amendment 1 Addition of 4 new sites (Glasgow, Northwick Park, Inverness, Doncaster)
17 January 2018	Substantial Amendment 2 Addition of 2 new sites (Aberdeen, Leicester)
21 March 2018	Substantial Amendment 3 Change of PI at 2 sites (Bradford, Aberdeen)
30 April 2018	Substantial Amendment 4 SPC updated, study cards added, study packs updated
28 May 2018	Substantial Amendment 5 Addition of 6 new sites (Winchester, Luton, Sandwell, Calderdale, Sheffield, Wolverhampton)
12 September 2018	Substantial Amendment 6 Addition of second Participant Invitation letter and Addition of 4 sites (Southampton, Musgrove Park, Devon, Homerton)
13 February 2019	Substantial Amendment 7 Updates to central follow-up documents and PI change (Northwick Park)
22 March 2019	Substantial Amendment 8 PI change St George's
12 June 2019	Substantial Amendment 9 PI change Wolverhampton
16 August 2019	Substantial Amendment 10 PI change Nottingham+ Inverness, minor updates to structured questionnaires
13 February 2020	Substantial Amendment 11 Clarification of exclusion criteria, Clarification of Adverse Event reporting requirements, Addition of central blinded review of Serious Adverse Events, Other minor changes to the protocol and the Structured Questionnaire

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	In line with Sponsor guidance, recruitment was halted on 17Mar2020 due to the COVID-19 pandemic . LACI-2 received Sponsor approval to restart recruitment on 10Jun2020 and all sites were asked to complete the restart checklist when they had capacity to restart.	10 June 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Open label design may facilitate bias, however, follow-up co-ordinators were blinded. Recruitment and follow-up at sites was affected by the COVID pandemic. As a factorial trial, comparison of the combination of drugs versus none was underpowered.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33072884>

<http://www.ncbi.nlm.nih.gov/pubmed/37222252>