



## Clinical trial results: Preventing cognitive decline and dementia from cerebral small vessel disease

### Summary

EudraCT number	2015-001953-33
Trial protocol	GB
Global end of trial date	31 July 2018

### Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019
Summary attachment (see zip file)	Fronteirs paper (fneur-10-00723.pdf) EClinical Medicine paper (1-s2.0-S2589537019300586-main.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	PrevSVD-2015
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#### Additional study identifiers

ISRCTN number	ISRCTN12580546
ClinicalTrials.gov id (NCT number)	NCT02481323
WHO universal trial number (UTN)	-
Other trial identifiers	Alzheimer's Society: 252 (AS-PG-14-033)

Notes:

#### Sponsors

Sponsor organisation name	University of Edinburgh
Sponsor organisation address	Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Trial Manager (Kirsten Shuler), University of Edinburgh, 44 131 465 9599, joanna.wardlaw@ed.ac.uk
Scientific contact	Prof Joanna Wardlaw, University of Edinburgh, 44 131 465 9599, joanna.wardlaw@ed.ac.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	17 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2017
Global end of trial reached?	Yes
Global end of trial date	31 July 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

We propose to do a small clinical trial to test how well Cilostazol and ISMN are tolerated by lacunar stroke patients when given individually or in combination, at increasing doses. We will monitor symptoms like headache, heart thumping, dizziness, bruising, other brain and leg symptoms, to see how patients find taking the drugs.

Protection of trial subjects:

Participants take trial medication for 11 weeks. The dose is increased, in weekly increments over two to three weeks as tolerated, sustained until eight weeks post-randomization, then decreased gradually over two weeks and stopped. The escalating dose is designed to reduce potential adverse effects following initiation of cilostazol and is standard for ISMN. Gradual dose reduction aims to prevent large hemodynamic changes on cessation of medication

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

Notes:

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**Subjects enrolled per age group**

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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)	27
From 65 to 84 years	27

85 years and over	3
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

Number of subjects started	57
Number of subjects completed	57

### Period 1

Period 1 title	treatment phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

To maintain blinding of participants, prior to the start of the trial, the Investigational Supplies Group (ISG), an independent arm of the Research and Development Office, NHS Lothian, removed study medications from their original blister packs and placed them in bottles labelled 'Drug A' or 'Drug B', a process which was approved by the Medicines and Healthcare Regulatory Agency.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	cilostazol

Arm description:

cilostazol alone, 50 mg twice daily, increasing to 100 mg twice daily

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

Dosage and administration details:

50mg twice daily increasing to 100mg twice daily

<b>Arm title</b>	ISMN
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Arm description:

ISMN alone, 25 mg once daily increasing to 25 mg twice daily

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

Dosage and administration details:

25mg od increasing to 25mg bd

<b>Arm title</b>	both, immediate start
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Arm description:

Cilostazol and ISMN combined, started immediately, ISMN given first

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

Dosage and administration details:

50mg twice daily increasing to 100mg twice daily

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

Dosage and administration details:

25mg od increasing to 25mg bd

<b>Arm title</b>	both, delayed
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Arm description:

cilostazol and ISMN combined, start delayed for three weeks, cilostazol given first.

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

Dosage and administration details:

50mg twice daily increasing to 100mg twice daily

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

Dosage and administration details:

25mg od increasing to 25mg bd

<b>Number of subjects in period 1</b>	cilostazol	ISMN	both, immediate start
Started	13	15	14
Completed	13	15	14
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

<b>Number of subjects in period 1</b>	both, delayed
Started	15
Completed	14
Not completed	1
Consent withdrawn by subject	1



## Baseline characteristics

### Reporting groups

Reporting group title	treatment phase
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Reporting group description: -

Reporting group values	treatment phase	Total	
Number of subjects	57	57	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	66.1		
standard deviation	± 11.1	-	
Gender categorical			
Units: Subjects			
Female	18	18	
Male	39	39	

### Subject analysis sets

Subject analysis set title	analysis set
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:  
one patient withdrew from study

Reporting group values	analysis set		
Number of subjects	56		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			

From 65-84 years 85 years and over			
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Age continuous Units: years arithmetic mean standard deviation	66.1 ± 11.1		
Gender categorical Units: Subjects			
Female	999		
Male	999		



## End points

### End points reporting groups

Reporting group title	cilostazol
Reporting group description:	cilostazol alone, 50 mg twice daily, increasing to 100 mg twice daily
Reporting group title	ISMN
Reporting group description:	ISMN alone, 25 mg once daily increasing to 25 mg twice daily
Reporting group title	both, immediate start
Reporting group description:	Cilostazol and ISMN combined, started immediately, ISMN given first
Reporting group title	both, delayed
Reporting group description:	cilostazol and ISMN combined, start delayed for three weeks, cilostazol given first.
Subject analysis set title	analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	one patient withdrew from study

### Primary: proportion of patients reaching target dose

End point title	proportion of patients reaching target dose
End point description:	The primary outcome was the proportion of participants achieving target dose by the end of the eight-week trial period, assessed by structured questionnaire
End point type	Primary
End point timeframe:	8 weeks from randomisation

End point values	cilostazol	ISMN	both, immediate start	both, delayed
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	14	14
Units: persons reaching target dose	3	8	5	5

End point values	analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: persons reaching target dose	21			

## Statistical analyses

<b>Statistical analysis title</b>	SAP
Statistical analysis description: provided in the study protocol at <a href="https://doi.org/10.1177/1747493017731947">https://doi.org/10.1177/1747493017731947</a>	
Comparison groups	ISMN v both, immediate start v cilostazol v both, delayed
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	< 0.05 <sup>[2]</sup>
Method	difference in proportions
Parameter estimate	Odds ratio (OR)
Point estimate	3.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	14.46
Variability estimate	Standard deviation

Notes:

[1] - safety and tolerability

[2] - ... in proportion reaching target dose

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

baseline, treatment phase

Adverse event reporting additional description:

patient self report at weekly FU

Assessment type	Systematic
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### Dictionary used

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Dictionary name	physician self compl
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Dictionary version	1
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Frequency threshold for reporting non-serious adverse events: 1.8 %

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### 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: Symptoms were common without trial medication. In the week prior to randomisation, the following symptoms were experienced: headache 30%; palpitations 20%; dizziness 40%; loose stools 30%; nausea 15%; dyspepsia 45%; bruising 20%; bleeding from mucous membranes 15%; and rash 9%. Following drug initiation, there was a slight increase in headache, palpitations, dizziness, loose stools, nausea, followed by a return to baseline levels with continued trial drug (Fig. 3; Table 2; Supplementary Fig. S3)

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31317131>

<http://www.ncbi.nlm.nih.gov/pubmed/31333572>

<http://www.ncbi.nlm.nih.gov/pubmed/28906205>