Clinical trial results:
A Calcium channel or Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker Regimen to reduce Blood pressure variability in acute ischaemic Stroke (CAARBS): A Feasibility Trial

Summary

EudraCT number	2017-002560-41
Trial protocol	GB
Global end of trial date	31 March 2019

Results information

Result version number	v1 (current)
This version publication date	03 December 2019
First version publication date	03 December 2019

Trial information

Trial identification

Sponsor protocol code	0611

Additional study identifiers

ISRCTN number	ISRCTN10853487
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Leicester General Hospital, Gwendolen Road, Leicester, United Kingdom, LE5 4PW
Public contact	Professor Thompson Robinson, University of Leicester, +44 01162523182, tgr2@leicester.ac.uk
Scientific contact	Professor Thompson Robinson, University of Leicester, +44 01162523182, tgr2@leicester.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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2019
Global end of trial reached?	Yes
Global end of trial date	31 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this feasibility study, patient recruitment and reasons for non-eligibility will be recorded. Accordingly, a screening log of all patients referred to the stroke services will be collected, and the reasons for non-inclusion in the study recorded.

Protection of trial subjects:

Subjects randomised to receive an angiotensin converting enzyme inhibitor or angiotensin receptor blocker had a blood test to monitor their renal function at the first follow-up visit, in line with standard clinical practise.

Background therapy:

Participants in both arms of the trial received standard stroke secondary prevention treatment in addition to the investigational treatment.

Evidence for comparator:

Work exploring the effects of commonly used antihypertensive medications in patients with hypertension has indicated that different classes of antihypertensive medication have different effects on the variability of blood pressure despite having similar impacts on average blood pressure levels. Specifically, blood pressure variability is reduced by calcium channel blockers, but increased by angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Furthermore, these differential effects on blood pressure variability correlate with the risk of stroke seen in patients taking these medications.

Actual start date of recruitment	01 September 2017
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: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment for the trial commenced on 3rd January 2018 and was undertaken at three sites within the UK. The trial closed to recruitment on 31st December 2018.

Pre-assignment

Screening details:

All patients presenting to stroke services at the involved trial sites (both in-patient and out-patient services at two of the sites and only out-patients at one site) were screened for potential inclusion in the trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	CCB arm

Arm description:

Patients randomised to this arm were allocated to treatment with a medication from the class dihydropyridine calcium channel blockers, with the specific choice of medication from within that class being at the discretion of the treating physician.

Arm type	Experimental
Investigational medicinal product name	Dihydropyridine calcium channel blocker
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administer orally once daily for the duration of the trial. To be started at the introductory dose and titrated up at the first follow-up visit if blood pressure remained above the pre-specified target value.

Arm title	ACEI/ARB arm

Arm description:

Patients randomised to this arm were allocated to treatment with a medication from the class angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, with the specific choice of medication from within the allocated class being at the discretion of the treating physician.

Arm type	Active comparator
Investigational medicinal product name	Angiotensin-converting enzyme inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally once daily for the duration of the trial. To be commenced at the introductory dose and titrated up at the first follow-up visit if blood pressure was above the pre-specified target value.

Investigational medicinal product name	Angiotensin receptor blocker
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally once daily for the duration of the trial. To be commenced at the introductory dose and titrated up at the first follow-up visit if blood pressure was above the pre-specified target value.

Number of subjects in period 1	CCB arm	ACEI/ARB arm
Started	6	8
Completed	4	5
Not completed	2	3
Screening failure	1	1
Consent withdrawn by subject	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CCB arm
Reporting group description:	
Patients randomised to this arm were allocated to treatment with a medication from the class dihydropyridine calcium channel blockers, with the specific choice of medication from within that class being at the discretion of the treating physician.	
Reporting group title	ACEI/ARB arm
Reporting group description:	
Patients randomised to this arm were allocated to treatment with a medication from the class angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, with the specific choice of medication from within the allocated class being at the discretion of the treating physician.	

Reporting group values	CCB arm	ACEI/ARB arm	Total
Number of subjects	6	8	14
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	74.8	64.9	
standard deviation	± 4.2	± 9.1	-
Gender categorical Units: Subjects			
Female	1	3	4
Male	4	4	8
Not recorded	1	1	2
Ethnicity categorical Units: Subjects			
White - British	4	6	10
White - other	1	1	2
Not recorded	1	1	2
Diagnosis categorical Units: Subjects			
Stroke	2	4	6
TIA	3	3	6
Not recorded	1	1	2
Smoking status categorical Units: Subjects			

Never smoked	2	2	4
Ex-smoker	3	2	5
Current smoker	0	3	3
Not recorded	1	1	2
Past medical history of hypertension categorical Units: Subjects			
Yes	3	1	4
No	2	6	8
Not recorded	1	1	2
Past medical history of diabetes categorical Units: Subjects			
Yes	1	0	1
No	4	7	11
Not recorded	1	1	2
Body mass index continuous Units: Kg/m2			
arithmetic mean	28.2	27.1	
standard deviation	± 4.6	± 5.8	-
Alcohol consumption continuous Units: units/week			
median	5	14	
inter-quartile range (Q1-Q3)	0 to 17	12 to 38	-
Mean enhanced clinic SBP continuous Units: mmHg			
arithmetic mean	163.6	152.7	
standard deviation	± 17.3	± 14.5	-
Mean enhanced clinic DBP continuous Units: mmHg			
arithmetic mean	81.8	83.1	
standard deviation	± 5.9	± 6.5	-
Standard deviation of enhanced clinic SBP continuous Units: mmHg			
arithmetic mean	8.4	6.8	
standard deviation	± 5.2	± 5.3	-
Standard deviation of enhanced clinic DBP continuous Units: mmHg			
arithmetic mean	5.6	6.0	
standard deviation	± 3.0	± 3.4	-
Coefficient of variation of enhanced clinic SBP continuous Units: percent			
arithmetic mean	4.9	4.5	
standard deviation	± 2.6	± 3.4	-
Coefficient of variation of enhanced clinic DBP continuous Units: percent			
arithmetic mean	7.0	7.2	
standard deviation	± 3.9	± 4.0	-
Mean beat-to-beat SBP continuous			

Units: mmHg			
arithmetic mean	156.6	151.0	
standard deviation	± 5.7	± 11.9	-
Mean beat-to-beat DBP continuous			
Units: mmHg			
arithmetic mean	79.8	82.6	
standard deviation	± 7.1	± 6.1	-
Standard deviation of beat-to-beat SBP continuous			
Units: mmHg			
arithmetic mean	9.9	9.2	
standard deviation	± 3.9	± 5.5	-
Standard deviation of beat-to-beat DBP continuous			
Units: mmHg			
arithmetic mean	5.2	5.1	
standard deviation	± 2.2	± 2.4	-
Coefficient of variation of beat-to-beat SBP continuous			
Units: percent			
arithmetic mean	6.3	6.0	
standard deviation	± 2.5	± 2.6	-
Coefficient of variation of beat-to-beat DBP continuous			
Units: percent			
arithmetic mean	6.6	6.3	
standard deviation	± 2.6	± 3.0	-

End points

End points reporting groups

Reporting group title	CCB arm

Reporting group description:

Patients randomised to this arm were allocated to treatment with a medication from the class dihydropyridine calcium channel blockers, with the specific choice of medication from within that class being at the discretion of the treating physician.

Reporting group title	ACEI/ARB arm

Reporting group description:

Patients randomised to this arm were allocated to treatment with a medication from the class angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, with the specific choice of medication from within the allocated class being at the discretion of the treating physician.

Primary: Feasibility of recruitment and retention

End point title	Feasibility of recruitment and retention[1]

End point description:

Firstly, the proportion of patients screened who were eligible for, and agreed to participate in the trial was recorded from the screening logs and is presented in the CONSORT flow diagram. Reasons for ineligibility were also assessed and quantified, and are presented in the accompanying table. Secondly, the rate of retention in the trial was assessed by recording the number of recruited participants who did and did not complete the trial follow-up period.

End point type	Primary

End point timeframe:

The number of patients screened who were recruited to the trial and the number of recruited participants who completed the trial was assessed over the whole trial period (15 months).

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: As this was a feasibility trial only descriptive analyses were carried out, with no formal statistical testing of any of the primary or secondary end-points.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: Number of participants				
Completed the trial	4	5		
Did not complete the trial	2	3		

Attachments (see zip file)	CONSORT flow diagram/Figure 1 CAARBS CONSORT Flow Table of reasons for exclusion.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance with trial treatment

End point title	Compliance with trial treatment

End point description:

Compliance was assessed using a self-report questionnaire. If participants were taking the trial medication >80% of the time then they were considered to be compliant.

End point type	Secondary

End point timeframe:

Compliance with trial treatment was assessed in each participant who completed the three month follow-up period.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: Number of participants				
>80% compliant	4	4		
<80% compliant	0	1		
Not recorded	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Completion rate of enhanced clinic blood pressure measurements

End point title	Completion rate of enhanced clinic blood pressure measurements

End point description:

End point type	Secondary

End point timeframe:

Compliance with trial measurement methods was assessed by recording completion rates of each blood pressure measurement over the three month follow-up period.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: Number of participants				
Complete	4	5		
Incomplete	0	0		
Not recorded	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Completion rate of beat-to-beat blood pressure measurements

End point title	Completion rate of beat-to-beat blood pressure measurements

End point description:

End point type	Secondary

End point timeframe:

Compliance with trial measurement methods was assessed by recording completion rates of each blood pressure measurement over the three month follow-up period.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: Number of participants				
Complete	4	3		
Incomplete	0	2		
Not recorded	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Standard deviation of enhanced clinic systolic blood pressure variability after three months

End point title	Standard deviation of enhanced clinic systolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mmHg				
arithmetic mean (standard deviation)	5.1 (± 2.1)	3.9 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Standard deviation of enhanced clinic diastolic blood pressure variability after three months

End point title	Standard deviation of enhanced clinic diastolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mmHg				
arithmetic mean (standard deviation)	4.3 (± 2.2)	3.1 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Coefficient of variation of enhanced clinic systolic blood pressure variability after three months

End point title	Coefficient of variation of enhanced clinic systolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent				
arithmetic mean (standard deviation)	4.0 (± 1.7)	3.1 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Coefficient of variation of enhanced clinic diastolic blood pressure

variability after three months	
End point title	Coefficient of variation of enhanced clinic diastolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent				
arithmetic mean (standard deviation)	5.8 (± 2.7)	4.3 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Standard deviation of beat-to-beat systolic blood pressure variability after three months

End point title	Standard deviation of beat-to-beat systolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mmHg				
arithmetic mean (standard deviation)	6.2 (± 3.0)	8.7 (± 5.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Standard deviation of beat-to-beat diastolic blood pressure variability after three months

End point title	Standard deviation of beat-to-beat diastolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mmHg				
arithmetic mean (standard deviation)	2.8 (± 1.4)	3.9 (± 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Coefficient of variation of beat-to-beat systolic blood pressure variability after three months

End point title	Coefficient of variation of beat-to-beat systolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent				
arithmetic mean (standard deviation)	4.5 (± 2.1)	6.0 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Coefficient of variation of beat-to-beat diastolic blood pressure variability after three months

End point title	Coefficient of variation of beat-to-beat diastolic blood pressure variability after three months

End point description:

End point type	Secondary

End point timeframe:

Blood pressure variability was assessed at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent				
arithmetic mean (standard deviation)	3.8 (± 1.8)	4.9 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Modified Rankin score at three months

End point title	Modified Rankin score at three months

End point description:

End point type	Other pre-specified

End point timeframe:

Functional outcome was assessed using the modified Rankin score at three month follow-up.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mRS points				
median (inter-quartile range (Q1-Q3))	0 (0 to 1)	0 (0 to 1)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Montreal Cognitive Assessment score at three months

End point title	Montreal Cognitive Assessment score at three months

End point description:

End point type	Other pre-specified

End point timeframe:

Cognition was assessed using the Montreal Cognitive Assessment at the three month follow-up visit.

End point values	CCB arm	ACEI/ARB arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: MoCA points				
arithmetic mean (standard deviation)	23.5 (± 2.7)	23.6 (± 3.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Data on adverse events was collected over the whole three month follow-up period for each participant. Only serious adverse events were reported in this feasibility trial.

Adverse event reporting additional description:

Data regarding adverse events were collected by research staff initiated questionnaire at each trial follow-up visit. There were no serious adverse events recorded during the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0.0

Reporting groups

Reporting group title	CCB arm

Reporting group description:

Patients randomised to this arm were allocated to treatment with a medication from the class dihydropyridine calcium channel blockers, with the specific choice of medication from within that class being at the discretion of the treating physician.

Reporting group title	ACEI/ARB arm

Reporting group description:

Patients randomised to this arm were allocated to treatment with a medication from the class angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, with the specific choice of medication from within the allocated class being at the discretion of the treating physician.

Serious adverse events	CCB arm	ACEI/ARB arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CCB arm	ACEI/ARB arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	

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 data on serious adverse events was collected in this feasibility trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2018	A substantial amendment was made to the trial eligibility criteria in order to try and improve recruitment figures. This was done following discussion with the Trial Management Group and Trial Steering Committee based on analysis of screening log data. Specifically, the inclusion criteria which stipulated that patients should be recruited within 72 hours of the qualifying clinical event (i.e. ischaemic stroke or transient ischaemic attack) was altered to allow inclusion of patients up to 7 days following the qualifying clinical event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30782930