



Clinical trial results:

An open label randomised controlled trial investigating the effect of donepezil on regional cerebral blood flow in adults with aneurysmal subarachnoid haemorrhage.

Summary

EudraCT number	2013-002457-30
Trial protocol	GB
Global end of trial date	10 November 2016

Results information

Result version number	v1 (current)
This version publication date	02 December 2019
First version publication date	02 December 2019
Summary attachment (see zip file)	End of Trial Form (JREODOC0077 declaration_end_trial_form CTIMPs-signed.pdf)

Trial information

Trial identification

Sponsor protocol code	13.0099
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	St Georges University of London
Sponsor organisation address	Cranmer Terrace, London, United Kingdom, SW17 0QT
Public contact	Dr Jeremy B Madigan, St George's Univeristy of London, 0044 02087254481, jeremy.madigan@nhs.net
Scientific contact	Dr Jeremy B Madigan, St George's Univeristy of London, 0044 02087254481, jeremy.madigan@nhs.net

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	10 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2016
Global end of trial reached?	Yes
Global end of trial date	10 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To measure the effects of donepezil on regional cerebral blood flow following aneurysmal subarachnoid haemorrhage

Secondary objectives

To assess whether the administration of donepezil to study participants with acute SAH:

I. Is safe.

II. Is tolerable for 21 days.

Protection of trial subjects:

The data monitoring committee will review the following trial data after the enrolment of the first 10 participants, and for every 20 participants in the trial after that.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2013
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: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	13
From 65 to 84 years	6

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Clinical history and examination as part of routine care, including medication and allergy history. Plain CT head and CT Angiogram. Bloods: Urea & electrolytes, liver function tests. Pregnancy test for potential female participants with child-bearing potential.

Pre-assignment period milestones

Number of subjects started	19
Number of subjects completed	19

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:

Neuroradiologist blinded to primary endpoint

Arms

Are arms mutually exclusive?	Yes
Arm title	Donepezil

Arm description: -

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

Dosage and administration details:

To those randomised to the donepezil arm, the first dose will be a loading dose of 20mg donepezil in suspension given via nasogastric tube under general anaesthesia. Subsequent doses will be 5mg donepezil once daily given orally by either dissolving or dispersing on the tongue or administered via a nasogastric tube, depending on the conscious level and safety of swallow for each participant. Doses should be taken at the same time each day preferably in the evening. All trial participants will receive donepezil for a total of 21 days, to cover the vasospasm 'at risk' period.

Arm title	Control
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Arm description: -

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

Number of subjects in period 1	Donepezil	Control
Started	10	9
Overall trial	9	9
Completed	9	9
Not completed	1	0
Adverse event, serious fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title

Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	19	19	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	13	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	8	8	

End points

End points reporting groups

Reporting group title	Donepezil
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Primary: Mean cerebral blood flow (mL/100g/min

End point title	Mean cerebral blood flow (mL/100g/min ^{[1][2]}
End point description: Xenon CT Perfusion scans	
End point type	Primary
End point timeframe: At least 3 hours following the first 20mg loading dose of Donepezil	

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 analysis was not reported due to low number of recruited patients.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis was not reported due to low number of recruited patients.

End point values	Donepezil			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mL/100g/min				
number (not applicable)	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

To report Serious Adverse Events to Sponsor within 24 hours of notification. All Adverse Events to be recorded on Adverse Event log.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	0

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

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: See adverse events attached.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2013	Concerns were raised by the REC about the safety of the single 20mg Donepezil dose, the protocol has been amended such that an interim analysis will be performed by a data monitoring committee after enrolment of the first 10 participants. This will be to investigate the occurrence of defined adverse events in relation to donepezil administration.
09 April 2014	Addition of Exclusion criteria 5.2 for requirement of FiO2 > 0.6 within protocol Additional section within protocol added 8.7.2.1 'technical criteria for participant replacement' Additional section added within protocol 8.7.2.2 ' Clinical criteria for participant replacement'
12 December 2014	Removal of CT angiogram performed following aneurysm coiling
22 September 2015	Temporary Halt

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 November 2016	The trial centre has installed a new CT scanner which is not compatible with the Xenon analysis software (despite reassurances from the CT manufacturer to the contrary). It is not possible to recruit any further subjects as we can no longer acquire primary endpoint data.	-

Notes:

Limitations and caveats

None reported