Clinical trial results:
Perfusion by Arterial Spin labelling following Single dose Tadalafil In Small vessel disease

Summary

EudraCT number	2015-001235-20
Trial protocol	GB
Global end of trial date	25 January 2018

Results information

Result version number	v1 (current)
This version publication date	03 June 2022
First version publication date	03 June 2022

Trial information

Trial identification

Sponsor protocol code	14.0189

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02450253
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	St George's University of London
Sponsor organisation address	Cranmer Terrace, London, United Kingdom,
Public contact	Atticus Hainsworth , St George's University of London, 44 02087253516, ahainswo@sgul.ac.uk
Scientific contact	Atticus Hainsworth , St George's University of London, 44 02087253516, ahainswo@sgul.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	13 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2018
Global end of trial reached?	Yes
Global end of trial date	25 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does Tadalafil increase blood flow in deep brain tissue?

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 65
Worldwide total number of subjects	65
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)	32
From 65 to 84 years	32
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

65 assessed for eligibility, 65 randomised

Pre-assignment

Screening details:

65 assessed for eligibility, 65 randomised

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Allocated to tadalafil at Visit 1, placebo at Visit 2

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

Dosage and administration details:

20mg

Arm title	Group 2

Arm description:

Allocated to placebo at Visit 1, tadalafil at Visit 2

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

Dosage and administration details:

20mg

Number of subjects in period 1	Group 1	Group 2
Started	35	30
Completed	31	24
Not completed	4	6
Physician decision	1	3
Consent withdrawn by subject	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	65	65	
Age categorical Units: Subjects			
Adults (18-90years)	65	65	
Age continuous Units: years arithmetic mean standard deviation	 66.7 ± 8.7	 -	
Gender categorical Units: Subjects			
Female Male	19 46	19 46	
MoCA score			
Scoring in MoCA ranges from0 to 30, with a score of 26 or higher indicating normal cognitive ability. These cores have been adjusted for educational level (+1 if the participant had 12 or more years of education).			
Units: Score arithmetic mean standard deviation	 25.4 ± 3.4	 -	
Time from stroke to consent Units: Months arithmetic mean standard deviation	 16 ± 17.6	 -	
Systolic blood pressure Units: mm Hg arithmetic mean standard deviation	 145 ± 16.6	 -	

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description: Allocated to tadalafil at Visit 1, placebo at Visit 2	
Reporting group title	Group 2
Reporting group description: Allocated to placebo at Visit 1, tadalafil at Visit 2	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: All participants who received placebo	
Subject analysis set title	Tadalafil
Subject analysis set type	Full analysis
Subject analysis set description: All participants who received Tadalafil	

Primary: Changes in Deep gray matter CBF

End point title	Changes in Deep gray matter CBF[1]
End point description:	
End point type	Primary
End point timeframe: All MRI data were acquired from brain scans performed on a Tuesday or Thursday, pre-dosing scans between the hours of 10:00 a.m. and 12:00 p.m., and post-dosing scans from 2:00 p.m. to 5:00 p.m.	

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: Please see attached link for the publication

End point values	Placebo	Tadalafil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[2]	53[3]		
Units: ml/min/100g				
arithmetic mean (confidence interval 95%)	1.75 (0.74 to 2.76)	1.79 (0.71 to 2.88)		

Notes:

[2] - completed the arm

[3] - completed the arm

Statistical analyses

No statistical analyses for this end point

Primary: Changes in Normal appearing white matter CBF

End point title	Changes in Normal appearing white matter CBF[4]
End point description:	
End point type	Primary

End point timeframe:

All MRI data were acquired from brain scans performed on a Tuesday or Thursday, pre-dosing scans between the hours of 10:00 a.m. and 12:00 p.m., and post-dosing scans from 2:00 p.m. to 5:00 p.m.

Notes:

[4] - 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: Please see attached link for the publication

End point values	Placebo	Tadalafil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	53		
Units: ml/min/100g				
arithmetic mean (confidence interval 95%)	0.8 (0.14 to 1.47)	1.15 (0.49 to 1.80)		

Statistical analyses

No statistical analyses for this end point

Primary: Changes in White matter hyperintensities

End point title	Changes in White matter hyperintensities[5]

End point description:

End point type	Primary

End point timeframe:

All MRI data were acquired from brain scans performed on a Tuesday or Thursday, pre-dosing scans between the hours of 10:00 a.m. and 12:00 p.m., and post-dosing scans from 2:00 p.m. to 5:00 p.m.

Notes:

[5] - 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: Please see attached link for the publication

End point values	Placebo	Tadalafil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	53		
Units: ml/min/100g				
arithmetic mean (confidence interval 95%)	0.82 (0.48 to 1.12)	1.29 (0.21 to 2.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Total gray matter CBF

End point title	Changes in Total gray matter CBF

End point description:

End point type	Secondary

End point timeframe:

All MRI data were acquired from brain scans performed on a Tuesday or Thursday, pre-dosing scans between the hours of 10:00 a.m. and 12:00 p.m., and post-dosing scans from 2:00 p.m. to 5:00 p.m.

End point values	Placebo	Tadalafil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	53		
Units: ml/min/100g				
arithmetic mean (confidence interval 95%)	2.05 (0.93 to 3.17)	2.54 (1.48 to 3.61)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	DAIDS
Dictionary version	2.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tadalafil
Reporting group description: -	

Serious adverse events	Placebo	Tadalafil	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	Tadalafil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 65 (12.31%)	3 / 65 (4.62%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Faint, light headed			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Panic attack			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			

Hypoglycaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Left knee pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Infections and infestations			
Cold and sore throat			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Chest infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2015	Move Cognitive testing from V1 to V0 and amend Statistician details
09 November 2015	Adjust MRI acquisition timings Eligibility criteria adjusted to allow lower age limit 50 and lower CrCl 30ml/min
10 March 2016	PIC sites added Eligibility criteria adjusted & FBC sample added
05 July 2017	SiMPD V3 May 2017 to include expiration date change following manufacture of 2nd IMP batch Protocol v5 22nd May 2017 to include corrections throughout and clarification of AE reporting frame To also include notification to MHRA of changes brought about by SA02 in regards to inclusion criteria
02 August 2017	Increase Sample size from 54 to 90
06 September 2017	Update PIS and ICF following SmPC review (DSUR#2 preparation) with rare reports of sudden hearing loss and Visual Disturbances

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

See final report appendix for limitations

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35135037