Clinical trial results:
Improving cerebral blood flow and cognition in patient with cerebral small vessel disease. The ETLAS-2 Trial.

Summary

EudraCT number	2020-002329-27
Trial protocol	DK
Global end of trial date	23 September 2024

Results information

Result version number	v1 (current)
This version publication date	15 November 2025
First version publication date	15 November 2025

Trial information

Trial identification

Sponsor protocol code	ETLAS-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05173896
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Neurology, Copenhagen University Hospital - Herlev and Gentofte
Sponsor organisation address	Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
Public contact	Christina Kruuse, Copenhagen University Hospital - Herlev and Gentofte, 0045 38681233, christina.kruuse@regionh.dk
Scientific contact	Christina Kruuse, Copenhagen University Hospital - Herlev and Gentofte, 0045 38681233, christina.kruuse@regionh.dk

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	22 August 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2024
Global end of trial reached?	Yes
Global end of trial date	23 September 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

We aim to investigate the feasibility of daily tadalafil for three months compared to placebo in patients with cerebral small vessel disease and stroke/TIA.

Protection of trial subjects:

Safety and adverse events were monitored throughout the trial period. Participants had a phone number they could call throughout the day to contact study personnel in case of questions and adverse events.

Background therapy:

All participants received standard care medication.

Evidence for comparator:

Daily dosing with 20 mg tadalafil was tested against daily placebo for three months. Tadalafil is a known vasoactive substance which we wanted to test in a population with cerebral small vessel disease. Impaired vascular reactivity is a characteristic feature of cerebral small vessel disease.

Actual start date of recruitment	14 June 2022
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	29
From 65 to 84 years	44
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Recruitment began on June 14, 2022, and concluded on June 19, 2024.
All participants were recruited from the Capital Region of Denmark.

Pre-assignment

Screening details:

We prescreened patient records of previously admitted patients from the stroke department of four hospitals in the Capital Region of Denmark. Eligible patients were asked for interest and invited to an information and inclusion visit.
We prescreened 13 532 patients, of which 255 were asked for interest. We included 76 patients in total.

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, Monitor, Data analyst, Subject, Carer, Assessor

Blinding implementation details:

This trial was blinded and placebo-controlled, with a 1:1 allocation between oral daily tadalafil 20 mg or placebo. Randomization was conducted by the Capital Region Pharmacy in Denmark. Tadalafil and placebo were encapsulated in identical opaque capsules and packaged in identical containers, each labeled with a unique identification number. Upon inclusion, participants were assigned a randomization number to ensure blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tadalafil

Arm description:

Daily tadalafil for 3 months.

Arm type	Experimental
Investigational medicinal product name	Tadalafil Stada
Investigational medicinal product code	G04BE08
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tadalafil Stada, 20 mg, administered once daily in the morning, for three months.

Arm title	Placebo

Arm description:

Daily placebo for 3 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo, administered once daily in the morning, for three months.

Arm title	Excluded before treatment initiation

Arm description:

These participants were all in the placebo group, but they were excluded before treatment initiation due to unexpected MRI contraindications.

Arm type	Placebo, excluded
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo, administered once daily in the morning, for three months.

Number of subjects in period 1	Tadalafil	Placebo	Excluded before treatment initiation
Started	38	33	5
Completed	33	33	0
Not completed	5	0	5
Adverse event, non-fatal	5	-	-
Excluded due to MRI contraindications.	-	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Tadalafil
Reporting group description:	
Daily tadalafil for 3 months.	
Reporting group title	Placebo
Reporting group description:	
Daily placebo for 3 months.	
Reporting group title	Excluded before treatment initiation
Reporting group description:	
These participants were all in the placebo group, but they were excluded before treatment initiation due to unexpected MRI contraindications.	

Reporting group values	Tadalafil	Placebo	Excluded before treatment initiation
Number of subjects	38	33	5
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	15	1
From 65-84 years	23	17	4
85 years and over	2	1	0
Age continuous			
Units: years			
median	70	65	75
inter-quartile range (Q1-Q3)	61 to 75	60 to 75	65.5 to 75.5
Gender categorical			
Units: Subjects			
Female	13	7	0
Male	25	26	5

Reporting group values	Total		
Number of subjects	76		
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)	29		
From 65-84 years	44		
85 years and over	3		
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical Units: Subjects			
Female	20		
Male	56		

End points

End points reporting groups

Reporting group title	Tadalafil
Reporting group description:	
Daily tadalafil for 3 months.	
Reporting group title	Placebo
Reporting group description:	
Daily placebo for 3 months.	
Reporting group title	Excluded before treatment initiation
Reporting group description:	
These participants were all in the placebo group, but they were excluded before treatment initiation due to unexpected MRI contraindications.	

Primary: Treatment feasibility: Compliance

End point title	Treatment feasibility: Compliance[1]
End point description:	
Medication compliance rate ≥90% at the end of the trial (3 months follow-up).	
End point type	Primary
End point timeframe:	
3 months follow-up.	

Notes:

[1] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	33		
Units: number of participants				
Compliance ≥90%	26	31		
Compliance <90%	12	33		

Statistical analyses

Statistical analysis title	Binary logistic regression analysis
Statistical analysis description:	
Binary logistic regression analysis of compliance rate between groups.	
Comparison groups	Placebo v Tadalafil
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Regression, Logistic

Secondary: Systolic blood pressure

End point title	Systolic blood pressure[2]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[3]	33		
Units: mmHg				
median (inter-quartile range (Q1-Q3))				
Baseline	144 (137 to 157)	144 (134 to 154)		
Follow-up	139 (131 to 156)	140 (130 to 148)		

Notes:

[3] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic blood pressure

End point title	Diastolic blood pressure[4]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[4] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[5]	33		
Units: mmHg				
median (inter-quartile range (Q1-Q3))				
Baseline	85 (78 to 94)	87 (81 to 94)		
Follow-up	83 (74 to 88)	85 (79 to 90)		

Notes:

[5] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: Heart rate

End point title	Heart rate[6]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[6] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[7]	33		
Units: bpm				
median (inter-quartile range (Q1-Q3))				
Baseline	71 (65 to 77)	73 (64 to 82)		
Follow-up	72 (65 to 77)	71 (58 to 75)		

Notes:

[7] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: Montreal Cognitive Assessment (MoCA)

End point title	Montreal Cognitive Assessment (MoCA)[8]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[8] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[9]	33		
Units: points				
median (inter-quartile range (Q1-Q3))				
Baseline	27 (25 to 27)	27 (26 to 29)		
Follow-up	26 (24 to 27)	27 (26 to 29)		

Notes:

[9] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

End point title	Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[10]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[10] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[11]	33		
Units: points				
median (inter-quartile range (Q1-Q3))				
Baseline	3.13 (3.00 to 3.42)	3.06 (3.00 to 3.25)		
Follow-up	3.13 (3.00 to 3.50)	3.06 (3.00 to 3.19)		

Notes:

[11] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: Becks Depression Inventory II (BDI-II)

End point title	Becks Depression Inventory II (BDI-II)[12]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[12] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[13]	33		
Units: points				
median (inter-quartile range (Q1-Q3))				
Baseline	5 (2 to 10)	3 (1 to 11)		
Follow-up	4 (1 to 8)	3 (1 to 7)		

Notes:

[13] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue Severity Scale (FSS)

End point title	Fatigue Severity Scale (FSS)[14]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[14] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[15]	33		
Units: points				
median (inter-quartile range (Q1-Q3))				
Baseline	3.22 (2.33 to 5.11)	3.78 (2.56 to 4.78)		
Follow-up	3.61 (1.89 to 4.72)	3.11 (1.89 to 4.89)		

Notes:

[15] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: World Health Organization 5 Well-Being Index (WHO-5)

End point title	World Health Organization 5 Well-Being Index (WHO-5)[16]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[16] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[17]	33		
Units: points				
median (inter-quartile range (Q1-Q3))				
Baseline	72 (60 to 80)	74 (60 to 88)		
Follow-up	72 (66 to 82)	80 (64 to 88)		

Notes:

[17] - 38 at baseline and 33 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: White matter hyperintensity volume

End point title	MRI: White matter hyperintensity volume[18]

End point description:

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[18] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[19]	33		
Units: ml				
median (inter-quartile range (Q1-Q3))				
Baseline	12.6 (4.18 to 29.1)	6.86 (3.43 to 22.5)		
Follow-up	9.57 (4.59 to 22.2)	6.75 (3.45 to 21.2)		

Notes:

[19] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Incident DWI lesions

End point title	MRI: Incident DWI lesions[20]

End point description:

Number of DWI lesions and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[20] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[21]	33		
Units: Number of DWI lesions				
Baseline: DWI lesion - YES	7	1		
Baseline: DWI lesion - NO	31	32		
Follow-up: DWI lesion - YES	5	3		
Follow-up: DWI lesion - NO	27	30		
Delta -1	4	0		
Delta 0	26	31		
Delta 1	2	2		

Notes:

[21] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Lacunes

End point title	MRI: Lacunes[22]

End point description:

Number of lacunes and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[22] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[23]	33		
Units: Number of lacunes				
median (inter-quartile range (Q1-Q3))				
Baseline	2 (1 to 4)	2 (1 to 4)		
Follow-up	2 (1 to 5)	2 (1 to 4)		
Delta	0 (0 to 1)	0 (0 to 0)		

Notes:

[23] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Microbleeds

End point title	MRI: Microbleeds[24]

End point description:

Number of microbleeds and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[24] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[25]	33		
Units: Number of microbleeds				
median (inter-quartile range (Q1-Q3))				
Baseline	1 (0 to 3)	1 (0 to 5)		
Follow-up	1 (0 to 4)	1 (0 to 5)		
Delta	0 (0 to 0)	0 (0 to 0)		

Notes:

[25] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Cortical superficial siderosis

End point title	MRI: Cortical superficial siderosis[26]

End point description:

Presence of cortical superficial siderosis and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[26] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[27]	33		
Units: Present or not present				
Baseline: Yes	1	1		
Baseline: No	37	32		
Follow-up: Yes	0	2		
Follow-up: No	32	31		
Delta 0	32	32		
Delta 1	0	1		

Notes:

[27] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Central atrophy

End point title	MRI: Central atrophy[28]

End point description:

Central atrophy score and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[28] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[29]	33		
Units: Scale from 0-2				
Baseline: None	9	11		
Baseline: Moderate	28	22		
Baseline: Severe	1	0		
Follow-up: None	10	14		
Follow-up: Moderate	21	19		
Follow-up: Severe	1	0		
Delta -1	3	3		
Delta 0	26	30		
Delta 1	3	0		

Notes:
[29] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Global cortical atrophy scales score

End point title	MRI: Global cortical atrophy scales score[30]

End point description:
Global cortical atrophy scales score and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:
Baseline and follow-up visit (3 months).

Notes:
[30] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[31]	33		
Units: Scale from 0-3				
Baseline: 0: Normal volume	8	7		
Baseline: 1: Opening of sulci	23	22		
Baseline: 2: Volume loss of gyri	7	4		
Baseline: 3: Knife blade atrophy	0	0		
Follow-up: 0: Normal volume	7	8		
Follow-up: 1: Opening of sulci	20	20		
Follow-up: 2: Volume loss of gyri	5	5		
Follow-up: 3: Knife blade atrophy	0	0		
Delta -1	3	3		
Delta 0	25	27		
Delta 1	4	3		

Notes:
[31] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Periventricular WMH

End point title	MRI: Periventricular WMH[32]

End point description:
Periventricular WMH and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[32] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[33]	33		
Units: Scale from 0-3				
Baseline: Fazekas 0	1	1		
Baseline: Fazekas 1	14	17		
Baseline: Fazekas 2	10	7		
Baseline: Fazekas 3	13	8		
Follow-up: Fazekas 0	1	0		
Follow-up: Fazekas 1	11	19		
Follow-up: Fazekas 2	10	5		
Follow-up: Fazekas 3	10	9		
Delta -1	2	2		
Delta 0	28	28		
Delta 1	2	3		

Notes:

[33] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Deep WMH

End point title	MRI: Deep WMH[34]

End point description:

Deep WMH and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[34] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[35]	33		
Units: Scale from 0-3				
Baseline: Fazekas 0	1	2		
Baseline: Fazekas 1	14	17		
Baseline: Fazekas 2	10	8		
Baseline: Fazekas 3	13	6		

Follow-up: Fazekas 0	1	1		
Follow-up: Fazekas 1	10	18		
Follow-up: Fazekas 2	13	7		
Follow-up: Fazekas 3	8	7		
Delta -1	2	0		
Delta 0	28	31		
Delta 1	2	2		

Notes:

[35] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: EPVS basal ganglia and centrum semiovale

End point title	MRI: EPVS basal ganglia and centrum semiovale[36]

End point description:

EPVS basal ganglia and centrum semiovale and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[36] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[37]	33		
Units: Scale from 0-3				
Baseline: No EPVS	1	2		
Baseline: 1-10 EPVS (mild)	20	24		
Baseline: 11-20 EPVS (moderate)	11	6		
Baseline: 21- EPVS (frequent)	6	1		
Follow-up: No EPVS	2	2		
Follow-up: 1-10 EPVS (mild)	19	24		
Follow-up: 11-20 EPVS (moderate)	6	5		
Follow-up: 21-40 EPVS (frequent)	5	2		
Delta -1	6	0		
Delta 0	25	32		
Delta 1	1	1		

Notes:

[37] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: EPVS midbrain

End point title	MRI: EPVS midbrain[38]

End point description:

Visible EPVS in the midbrain and delta value (follow-up - baseline).

End point type	Secondary

End point timeframe:

Baseline and follow-up visit (3 months).

Notes:

[38] - 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: There is no data for the Arm: Excluded before treatment initiation. These participants were excluded before any intervention and assessment.

End point values	Tadalafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[39]	33		
Units: Visible or not visible				
Baseline: No EPVS visible	20	25		
Baseline: EPVS visible	18	8		
Follow-up: No EPVS visible	19	24		
Follow-up: EPVS visible	13	9		
Delta -1	4	1		
Delta 0	26	30		
Delta 1	2	2		

Notes:

[39] - 38 at baseline and 32 at follow-up.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion in the trial to the safety follow-up visit 2 weeks after treatment cessation.

Adverse event reporting additional description:

Adverse events were registered on a specific adverse events questionnaire. This questionnaire was reviewed during all physical visits and orally during all telephone visits.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	28.1

Reporting groups

Reporting group title	Tadalafil

Reporting group description:

Daily tadalafil for 3 months.

Reporting group title	Placebo

Reporting group description:

Daily placebo for 3 months.

Serious adverse events	Tadalafil	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)	0 / 33 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Death	Additional description: Sudden cardiac death.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Seizure	Additional description: Required admission at a local hospital for observation.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional	Additional description: Required admission at a local hospital for observation.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Cholelithiasis	Additional description: Required admission at a local hospital for observation.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chest pain	Additional description: Muscular chest pain that required admission at a local hospital for investigation and observation.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Tadalafil	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 38 (65.79%)	8 / 33 (24.24%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 38 (26.32%)	5 / 33 (15.15%)	
occurrences (all)	16	17	
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	7 / 38 (18.42%)	3 / 33 (9.09%)	
occurrences (all)	25	5	
Eye disorders			
Eye pain			
subjects affected / exposed	4 / 38 (10.53%)	2 / 33 (6.06%)	
occurrences (all)	13	2	
Gastrointestinal disorders			
Reflux gastritis			
subjects affected / exposed	17 / 38 (44.74%)	3 / 33 (9.09%)	
occurrences (all)	35	44	
Abdominal discomfort			
subjects affected / exposed	10 / 38 (26.32%)	3 / 33 (9.09%)	
occurrences (all)	23	3	
Abdominal pain			

subjects affected / exposed	4 / 38 (10.53%)	3 / 33 (9.09%)	
occurrences (all)	9	3	
Diarrhoea			
subjects affected / exposed	6 / 38 (15.79%)	0 / 33 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	1 / 38 (2.63%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	5 / 38 (13.16%)	4 / 33 (12.12%)	
occurrences (all)	8	4	
Dyspnoea			
subjects affected / exposed	1 / 38 (2.63%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Flushing	Additional description: Facial flushing.		
subjects affected / exposed	6 / 38 (15.79%)	3 / 33 (9.09%)	
occurrences (all)	36	3	
Erythema	Additional description: Local skin reddening and itching.		
subjects affected / exposed	2 / 38 (5.26%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Pain	Additional description: Muscle pain.		
subjects affected / exposed	13 / 38 (34.21%)	2 / 33 (6.06%)	
occurrences (all)	28	13	
Back pain			
subjects affected / exposed	8 / 38 (21.05%)	1 / 33 (3.03%)	
occurrences (all)	13	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Recruitment stopped before reaching the aimed 100 participants due to limited time in the funded trial period. This resulted in a smaller sample size than planned.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/40718899