



Clinical trial results:

Penumbral Rescue by Normobaric O=O Administration in Patients with Ischemic Stroke and Target Mismatch ProFile: A Phase II Proof-of-Concept Trial

Summary

EudraCT number	2017-001355-31
Trial protocol	BE CZ FI ES
Global end of trial date	22 August 2022

Results information

Result version number	v1 (current)
This version publication date	31 August 2023
First version publication date	31 August 2023
Summary attachment (see zip file)	Summary of Clinical Study Report (20230811_PROOF_final_clinical_study_report_V01.pdf)

Trial information

Trial identification

Sponsor protocol code	PROOF
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03500939
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University hospital Tuebingen
Sponsor organisation address	Hoppe-Seyler-Straße 3, Tuebingen, Germany,
Public contact	Department of Neurology and Stroke, University Hospital Tübingen, +49 1724682284, sven.poli@uni-tuebingen.de
Scientific contact	Department of Neurology and Stroke, University Hospital Tübingen, +49 1724682284, sven.poli@uni-tuebingen.de

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	08 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2022
Global end of trial reached?	Yes
Global end of trial date	22 August 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the PROOF trial is to investigate efficacy and safety of normobaric hyperoxygenation (NBHO) as a neuroprotective treatment in patients with acute ischemic stroke due to large vessel occlusion likely to receive endovascular mechanical thrombectomy (TBY) in a randomized controlled clinical phase IIB trial.

To demonstrate an effect of NBHO on penumbral salvage in ischemic stroke.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2018
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	Spain: 44
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Finland: 24
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 118
Worldwide total number of subjects	223
EEA total number of subjects	223

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)	60
From 65 to 84 years	125
85 years and over	38

Subject disposition

Recruitment

Recruitment details:

The study population for this trial included male and female patients aged 18 to ≥ 85 with ischemic stroke due to intracranial anterior circulation LVO.

Pre-assignment

Screening details:

From 17.08.2019 to 13.05.2022 233 of the initially planned 460 patients were enrolled in the PROOF-study. Patients were randomized 1:1.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor ^[1]

Blinding implementation details:

Clinical trial with blinded outcome assessment (PROBE design).

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment group

Arm description:

Normobaric oxygen therapy was started within 6 hours after certain stroke symptom onset (witnessed) or after symptom recognition (in case of wake-up or unknown onset stroke) and within 30 minutes after end of baseline brain imaging and applied until removal of guide catheter from sheath at the end of endovascular mechanical thromboectomy or for 4 hours if mechanical thromboectomy was not attempted or stopped prior to manipulation of intracranial anterior circulation large vessel occlusion.

Arm type	Experimental
Investigational medicinal product name	Oxygen for medical use
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Inhalation use

Dosage and administration details:

Oxygen used for medical purposes is a diatomic gas applied via the natural or an artificial airway in concentrations between 21 % (as in atmospheric air) and 100% depending on the type and severity of the disorder that necessitates oxygen supplementation.

Arm title	Control group
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Arm description:

Control arm: oxygen supplementation if oxygen saturation $\leq 94\%$ at 2 to 4L/min via nasal cannula according to guidelines of the European Stroke Organisation, or in case of mechanical thromboectomy-related ventilation, ventilation with an initial inspiratory oxygen fraction of 0,3 to be gradually increased if oxygen saturation $\leq 94\%$.

Arm type	Active comparator
Investigational medicinal product name	Oxygen for medical use
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Inhalation use

Dosage and administration details:

Oxygen used for medical purposes is a diatomic gas applied via the natural or an artificial airway in

concentrations between 21 % (as in atmospheric air) and 100% depending on the type and severity of the disorder that necessitates oxygen supplementation.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Staff that was involved in the emergency treatment of patients was not blinded.

Outcome-raters at the image core laboratory were blinded to the respective treatment as they did not receive any information about randomization and the prior clinical course.

Number of subjects in period 1	Treatment group	Control group
Started	112	111
Completed	93	91
Not completed	19	20
Adverse event, serious fatal	14	14
Consent withdrawn by subject	1	-
Other	3	3
Lost to follow-up	1	2
non compliance /medical reasons	-	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment group
Reporting group description:	
Normobaric oxygen therapy was started within 6 hours after certain stroke symptom onset (witnessed) or after symptom recognition (in case of wake-up or unknown onset stroke) and within 30 minutes after end of baseline brain imaging and applied until removal of guide catheter from sheath at the end of endovascular mechanical thromboectomy or for 4 hours if mechanical thromboectomy was not attempted or stopped prior to manipulation of intracranial anterior circulation large vessel occlusion.	
Reporting group title	Control group
Reporting group description:	
Control arm: oxygen supplementation if oxygen saturation $\leq 94\%$ at 2 to 4L/min via nasal cannula according to guidelines of the European Stroke Organisation, or in case of mechanical thromboectomy-related ventilation, ventilation with an initial inspiratory oxygen fraction of 0,3 to be gradually increased if oxygen saturation $\leq 94\%$.	

Reporting group values	Treatment group	Control group	Total
Number of subjects	112	111	223
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)	30	30	60
From 65-84 years	64	61	125
85 years and over	18	20	38
Age continuous			
Units: years			
median	75	76	
full range (min-max)	36 to 95	35 to 93	-
Gender categorical			
Units: Subjects			
Female	55	55	110
Male	57	56	113
Brain Imaging Method			
Units: Subjects			
MRI	11	9	20
CT	101	102	203
Side of LVO			
Units: Subjects			
Left	60	58	118
Right	52	53	105
LVO location			
Units: Subjects			
carotid-T	19	13	32

proximal M12-segment	40	41	81
distal M1-segment	27	28	55
M2/M3 segments	26	29	55
time window until randomization Units: Subjects			
known, <6h	95	86	181
unknown/wake up/>=6h	17	25	42
NIH Stroke Scale Score Units: Subjects			
5 and less	0	1	1
6-10	33	31	64
11-20	63	66	129
21 and more	16	13	29
Tandem stenosis Units: Subjects			
yes	18	13	31
no	94	98	192

End points

End points reporting groups

Reporting group title	Treatment group
Reporting group description: Normobaric oxygen therapy was started within 6 hours after certain stroke symptom onset (witnessed) or after symptom recognition (in case of wake-up or unknown onset stroke) and within 30 minutes after end of baseline brain imaging and applied until removal of guide catheter from sheath at the end of endovascular mechanical thromboectomy or for 4 hours if mechanical thromboectomy was not attempted or stopped prior to manipulation of intracranial anterior circulation large vessel occlusion.	
Reporting group title	Control group
Reporting group description: Control arm: oxygen supplementation if oxygen saturation $\leq 94\%$ at 2 to 4L/min via nasal cannula according to guidelines of the European Stroke Organisation, or in case of mechanical thromboectomy-related ventilation, ventilation with an initial inspiratory oxygen fraction of 0,3 to be gradually increased if oxygen saturation $\leq 94\%$.	

Primary: Core Volume

End point title	Core Volume ^[1]
End point description: Primary efficacy of normobaric oxygen therapy is determined by ischemic core growth in the normobaric oxygen therapy and control arms. ischemic core growth is defined as the change in core volume (mL) from baseline (determined on diffusion-weighted MRI, CT perfusion or CT angiography source images) to 24 hours (diffusion-weighted MRI).	
End point type	Primary
End point timeframe: 24h	
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: See the attached Clinical Trial Report.	

End point values	Treatment group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: mL				
number (not applicable)	105	109		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NIHSS

End point title	Change in NIHSS ^[2]
End point description: Key secondary outcome was the change in NIHSS from baseline to 24 hours. Further secondary efficacy outcomes include the mRS at 90 days, arterial oxygen pressure mechanical thromboectomy (or at 90 minutes), relative percent change in ischemic core volume from baseline to 24 hours and Barthel Index, Montreal Cognitive Assessment, Montgomery-Asberg Depression Rating Scale and the patient reported	

outcomes Stroke Impact Scale-16 and EuroQoL-5 Dimensions-5 Levels at 90 days.

End point type	Secondary
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End point timeframe:

24h

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: See the attached Clinical Trial Report.

End point values	Control group			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: n.n.				
number (not applicable)	111			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

90 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	4.0
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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: For the safety evaluation see the attached Clinical Trial Report

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2018	1) Protocol V1.1 Submitted via international step of VHP on 30.05.2018 to address the requested modifications from the participating competent authorities to obtain the approval after the first submission. The protocol was later approved in a national step by Belgium, Czech Republic, Finland, Germany and Spain
12 April 2019	2) Protocol V1.2 Submitted via international step of VHP on 12.04.2019 to combine the requested modifications from the participating competent authorities and Ethics Committees e.g integration of a risk-benefit analysis. The protocol was later approved in a national step by Belgium, Czech Republic, Finland, Germany and Spain
15 December 2019	3) Protocol V1.3 Submitted via international step of VHP on 15.12.2019 to simplify inclusion criteria to boost patient recruitment e.g. the extension of the therapeutic time window from 3 to 6 hours and the omitting of the upper age limit of previously 80 years, allowing enrollment of more distal M2/3 segment occlusions, and tandem stenoses. The protocol was later approved in a national step by Belgium, Czech Republic, Finland, Germany and Spain. The protocol was submitted outside the VHP procedure to French competent authorities and ethics committee. France requested some clarification in the wording of the protocol, which did not have any impact on the study conduct and design, so that a French specific protocol was created and approved.
01 December 2020	4) Temporary hold of patient recruitment The patient recruitment was temporarily suspended due to safety concerns (number of observed intracranial hemorrhages) after the data and safety monitoring board held their first meeting. The temporary hold was reported nationally to the competent authorities and ethics committees via a substantial amendment.
22 March 2021	5) Protocol V1.4 Submitted via international step of VHP on 22.03.2021. The protocol was modified following the recommendations from the DSMB and taking the updated current international acute ischemic stroke guidelines into account. Besides, the risk-benefit section was updated, the biomarker study simplified and the French modifications integrated. The protocol was later approved in a national step by the competent authorities and Ethic committees in Belgium, Czech Republic, Finland, France, Germany and Spain, so that new patients could be enrolled.
13 May 2022	6) Early study termination due to futility result of pre-specified interim analysis After the first 160 patients were enrolled and treated an pre-specified interim analysis was done carried out while the patient enrollment continued. The trial protocol foresees stopping the trial for futility if the direction of the effect for the primary endpoint favours the control arm. The data and safety monitoring board recommended to stop the patient recruitment, because there were no indications that the normobaric oxygen therapy is advantageous. At that point 223 of the initially planned 460 patients were enrolled in the PROOF study from 17.08.2019 (FPI) – 13.05.2022 (LPI)).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 December 2020	temporary interruption till may 2021	-

Notes:

Limitations and caveats

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

No reported limitations and caveats.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37515459>