# 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 |

**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 stidy 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 apllied until removal of guide catheter from sheath at the end of endovascular mechanical thromboectomy or for 4 hours if mechnaical 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 diatmoic gas applied via the natural or an artificial airway in concentrations between 21 % (as in athmosperic air) and 100% depending on he type and severity of the disorder that necessitates oxygen supplementation.

| | |
|---|---|
| **Arm title** | Control group |

Arm description:

Control arm: oxygen supplementation if oxygen saturation <= 94% at 2 to 4L/min via nasal cannula according to guidelines of the European Stroke Organsiation, 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 <= 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 diatmoic gas applied via the natural or an artificial airway in

concentrations between 21 % (as in athmosperic air) and 100% depending on he 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 blinmded. Outcome-raters at the image core laboratory were blinded to the respective tratment 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 apllied until removal of guide catheter from sheath at the end of endovascular mechanical thromboectomy or for 4 hours if mechnaical 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 <= 94% at 2 to 4L/min via nasal cannula according to guidelines of the European Stroke Organsiation, 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 <= 94%. | |

| Reporting group values | Treatment group | Control group | Total |
|---|---|---|---|
| Number of subjects | 112 | 111 | 223 |
| Age categorical<br>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<br>Units: years | | | |
| median | 75 | 76 | |
| full range (min-max) | 36 to 95 | 35 to 93 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 55 | 55 | 110 |
| Male | 57 | 56 | 113 |
| Brain Imaging Method<br>Units: Subjects | | | |
| MRI | 11 | 9 | 20 |
| CT | 101 | 102 | 203 |
| Side of LVO<br>Units: Subjects | | | |
| Left | 60 | 58 | 118 |
| Right | 52 | 53 | 105 |
| LVO location<br>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<br>Units: Subjects | | | |
| known, <6h | 95 | 86 | 181 |
| unknown/wake up/>=6h | 17 | 25 | 42 |
| NIH Stroke Scale Score<br>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<br>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 apllied until removal of guide catheter from sheath at the end of endovascular mechanical thromboectomy or for 4 hours if mechnaical 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 <= 94% at 2 to 4L/min via nasal cannula according to guidelines of the European Stroke Organsiation, 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 <= 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 vore volume (mL) from baseline (determined on diffsuion-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 24hurs. Further secondary efficacy outcomes include the mRS at 90days, 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 |
|---|---|

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 |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 4.0 |

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: 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<br>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<br>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<br>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 occlu-sions, and tandemstenoses. 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<br>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<br>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<br>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