Summary of Clinical Study Report

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

Name of investigational product:	Normobaric hyperoxygenation therapy (NBHO) Control: oxygen supplementation if oxygen saturation (SpO_2) ≤ 94% according to guidelines of the European Stroke Organisation (ESO)
Indication of study:	Acute ischemic stroke due to intracranial anterior circulation LVO MedDRA-code: 10061256 and 10055221 ICD-code: I63.3/4
Development phase of study:	Clinical Phase IIb
EudraCT Number:	2017-001355-31
Protocol identification code:	ClinicalTrials.gov number: NCT03500939
Date of the report:	11.08.2023
Version:	1.0
Coordinating Investigator (Principle Investigator)	PD Dr. med. Sven Poli University Hospital Tübingen, Dept. of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
Name of Sponsor	Eberhard-Karls University Tübingen Medical Faculty represented by University Hospital Tübingen and its Commercial Director: Dipl.-Volksw. Gabriele Sonntag, Geissweg 5, 72074 Tübingen, Germany
Sponsor´s delegated person	PD Dr. med. Sven Poli University Hospital Tübingen, Dept. of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany, Phone 0049 172 4682284, E-Mail: sven.poli@uni-tuebingen.de
Author(s) Study Report	PD Dr. med. Sven Poli University Hospital Tübingen, Dept. of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
Study initiation date (date of first enrolment)	17.08.2019
Date of early study termination (date of last completed)	22.08.2022

1 Name of Investigational Medicinal Product

Investigational medicinal products used
Oxygen (for medical use)
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.

2 Individual Study Table

Not applicable

3 Title of Study and Approvals

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

Trail Protocol Version 1.0 / 10.04.2018
Initially rejected from German lead EC on 26.07.2018 due to safety concerns.

Trail Protocol Version 1.1 / 30.05.2018
Protocol revision requested by VHP.

Trail Protocol Version 1.2 / 14.03.2019
Implementation of the requests of the Tübingen EC (i.e., inclusion of the reiterated risk-benefit-analysis in the trial protocol, separate ICF for biomarker sub study and update of ICF for main trial).

Trail Protocol Version 1.3 / 06.12.2019
Modifications to the inclusion criteria (above all, 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) and simplifications to the protocol.

Trial Protocol Version 1.4 / 17.03.2021
Update regarding to endovascular thrombectomy workflow and international acute ischemic stroke guidelines (perfusion imaging no longer mandatory); update of risk benefit section considering the most recent literature; simplification of biomarker sub-study.

VHP international	Protocol version 1.0 (10.04.2018)		Protocol version 1.1 (30.05.2018)		Protocol version 1.2 (14.03.2019)		Protocol version 1.3 (06.12.2019)		Protocol version 1.4 (17.03.2021)	
country	submission	approval	submission	approval	submission	approval	submission	approval	submission	approval
Germany	12.04.2018	N/A	30.05.2018	18.06.2018	12.04.2019	28.05.2019	15.12.2019	04.02.2020	19.03.2021	27.04.2021

VHP international step

VHP national	Protocol version **1.0** (10.04.2018)		Protocol version **1.1** (30.05.2018)		Protocol version **1.2** (14.03.2019)		Protocol version **1.3** (06.12.2019)		Protocol version **1.4** (17.03.2021)	
Country	submission	approval	submission	approval	submission	approval	submission	approval	submission	approval
Germany	N/A	N/A	22.06.2018	09.07.2018	29.05.2018	11.06.2019	06.02.2020	11.02.2020	03.05.2021	04.05.2021
Belgium	N/A	N/A	02.07.2018	10.07.2018	04.06.2019	13.06.2019	06.02.2020	13.02.2020	07.05.2021	28.05.2021
Czech Republic	N/A	N/A	04.07.2018	20.11.2018	03.06.2019	10.06.2019	10.02.2020	14.02.2020	04.05.2021	07.05.2021
Finland	N/A	N/A	03.07.2018	09.10.2018	31.05.2019	11.09.2019	14.02.2020	18.02.2020	29.04.2021	04.05.2021
France*	N/A	N/A	N/A	N/A	18.09.2019	N/A	18.02.2020	15.04.2020	07.05.2021	21.06.2021
Spain	N/A	N/A	06.07.2018	N/A	14.03.2019	12.11.2019	10.02.2020	18.02.2020	05.05.2021	02.06.2021

VHP national step to competent authorities. **Countries not participating in VHP*

Ethical Committee	Protocol version **1.0** (10.04.2018)		Protocol version **1.1** (30.05.2018)		Protocol version **1.2** (14.03.2019)		Protocol version **1.3** (06.12.2019)		Protocol version **1.4** (17.03.2021)	
Country	submission	approval	submission	approval	submission	approval	submission	approval	submission	approval
Germany	07.05.2018	12.02.2019	N/A	N/A	19.03.2019	02.04.2019	10.02.2020	19.02.2020	22.03.2021	08.04.2021 21.05.2021 Approval ICF changes
Belgium	N/A	N/A	N/A	N/A	06.12.2019	15.07.2020	08.09.2020	08.10.2020	10.05.2021	26.05.2021 19.07.2021* 26.07.2021
Czech Republic	N/A	N/A	27.08.2018	10.10.2018	07.08.2019	11.09.2019	17.02.2020	13.05.2020	05.05.2021	18.05.2021 02.06.2021 09.06.2021*
Finland	N/A	N/A	N/A	N/A	31.05.2019	10.10.2019	27.02.2020	25.03.2020	29.04.2021	10.06.2021
France	N/A	N/A	N/A	N/A	N/A	N/A	05.03.2020	23.07.2020	11.05.2021	14.06.2021 CNIL 13.08.2021
Spain	N/A	N/A	06.07.2018	N/A	27.06.2019	25.09.2019	10.02.2020	implicit	05.05.2021	26.05.2021

National ethical committees. *Lead EC

Switzerland

The Swiss protocol was adapted to reflect the Swiss regulations. Besides, the inclusion criteria und consenting procedure were slightly modified as requested by BASEC.

Switzerland	Protocol Version **1.4 CH** (27.05.2021)		Protocol Version **1.5 CH** (21.10.2021)		Protocol Version **1.6 CH** (03.12.2021)	
	submission	approval	submission	approval	submission	approval
Swissmedic	17.06.2021	03.09.2021	N/A	N/A	19.01.2022	07.03.2022
BASEC	17.08.2021	N/A	22.10.2021	N/A	17.12.2021	03.01.2022

Swiss protocol approval by competent authority (Swissmedic) and Ethics Committee (BASEC) in Switzerland

4 Investigators and Study Centers

Country	Investigators	Active, recruiting Study Centers
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Czech Republic	Prof. Robert Mikulik (National Coordinator)	Fakultni Nemocnice U SV. Anny V Brne, Pekarska 53, Brno 65691, Czech Republic
Finland	Prof. Daniel Strbian (National Coordinator)	Helsinki University Hospital, 15675350, Stenbackinkatu 9, Helsinki 00029, Finland
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	Prof. Michael Obadia	HOPITAL FONDATION Fondation Adolphe de Rothschild, 29, rue Manin, 75019 Paris, France
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Spain	Prof. Carlos A. Molina (National Coordinator)	Hospital Universitari Vall d´Hebron, Passeig de la Vall d'Hebron, 119-129, 08035 Barcelona, Spain
	Prof. Juan Francisco Arenillas	HCU Valladolid, Avenida Ramón y Cajal nº3 C.P.:47003 Valladolid, Spain
	Prof. Pere Cardona	Hospital Universitari de Bellvitge, 08907 L'Hospitalet de Llobregat, Barcelona, Spain

Country	Investigators	Initiated, non-recruiting Study Centres
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Czech Republic	Prof. Ivana Štětkářová	University Hospital Kralovske, Fakultní nemocnice Královské Vinohrady, Pavilon F., 3.p. Oddělení JIP, Šrobárova 50, 100 34 Praha 10, Czech Republic
Switzerland	Prof. Patrik Michel (National Coordinator)	Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, 1011 Lausanne, Switzerland
	Prof. Krassen Nedeltchev	Kantonspital Aarau, Neurologische Klinik, Tellstrasse, CH-5001 Aarau, Switzerland

Country	Investigators	Study Centres approved by ethics committees, never initiated
Belgium	Dr. Philippe Desfontaines	Clinique CHC MontLégia, Boulevard Patience et Beaujonc 2, 4000 Liège, Belgium
Czech Republic	Prof. Martin Kovář	Nemocnice Na Homolce (Homolka), Roentgenova 2, 150 30 Praha 5, Czech Republic
France	Prof. Marie-Hélène Mahagne	Service de Neurologie et Unité Neuro-Vasculaire, 4 Avenue Reine Victoria, 06003 Nice, France
Germany	Priv.-Doz. Patrick Schramm	Universitätsklinikum Giessen, Neurologische Klinik, Klinik Str. 33 35385 Giessen, Germany

5 Publications

Sven Poli et al. (2023) Penumbral Rescue by Normobaric O=O Administration in Patients with Ischemic Stroke and Target Mismatch ProFile (PROOF): Study Protocol of a Phase IIb Trial, International Journal of Stroke, accepted June 12,2023, Int J Stroke journal ID number: IJS-04-23-10906.R1, DOI: not yet available

Sven Poli et al. (2017) Normobaric hyperoxygenation: a potential neuroprotective therapy for acute ischemic stroke?, Expert Review of Neurotherapeutics, 17:12, 1131-1134, DOI: 10.1080/14737175.2017.1376657

6 Studied period (years)

- **Date of first enrolment:** 17.08.2019
- **Date of last completed visit of last patient:** 22.08.2022
- **Termination of study:** 13.05.2022
  After the first 160 patients were included in the study and treated., the prespecified interim analysis was started in February 2022 and was finalized in May 2022. The interim analysis was the basis for the DSMB meeting held on 13.05.2022. The DSMB recommended to stop the recruitment in the PROOF study due to futility.

7 Phase of Development

Clinical Phase IIb
The investigational medicinal product, i.e., oxygen is approved and used for many medical conditions.

8 Objectives

Ischemic stroke is caused by acute occlusion of cerebral arteries leading to interruption of blood flow and consequently of oxygen supply to brain tissue. Duration and severity of ischemia are primary determinants of brain tissue damage.[1] Because of the high energy demand of neurons and their limited capacity for energy storage, cellular hypoxia quickly leads to the breakdown of oxidative mitochondrial metabolism and anoxic cell death in the ischemic core. The less ischemic peripheral zone, the penumbra, is initially viable but will proceed to infarction unless there is timely reperfusion. It is particularly vulnerable to additional hemodynamic and metabolic challenges. Various cascades such as secondary hypoxia due to peri-infarct depolarization may aggravate tissue damage.[1]

So far, translational research has failed to establish brain-protective therapies in acute ischemic stroke, and revascularization of the occluded cerebral arteries by thrombolysis or mechanical thrombectomy is the only proven effective treatment.[2,3] Rapid demise of the penumbra, however, explains unfavorable outcomes in a substantial proportion of patients despite successful reperfusion.[3] To increase the number of patients eligible for revascularization and improve their outcomes, brain-protective "bridging" extending penumbral tissue survival ("freezing the penumbra") would be desirable.[4,5]
Neuronal energy production depends almost exclusively on oxidative phosphorylation in the mitochondria.[6] Although the brain represents only 2% of the body's weight, it consumes roughly 20% of the oxygen available to the whole body.[6,7] As the critical oxygen tension required for mitochondrial function is very low (1.5 mmHg),[7] improving oxygen delivery to ischemic-hypoxic tissue appears to be a plausible therapeutic concept to mitigate cell death.[5]
Consequently, the PROOF trial investigates normobaric oxygen therapy for brain-protective bridging until revascularization by mechanical thrombectomy in patients with acute ischemic stroke.

Main objective of the PROOF trial was to investigate efficacy and safety of normobaric oxygen therapy as a neuroprotective treatment in the acute phase of ischemic stroke with early reperfusion in a randomized controlled clinical trial.

The trial was designed as a proof-of-concept study, replicating insights from those preclinical studies in which normobaric oxygen therapy showed positive effects:

(1) We aimed for **near 100% oxygen** delivery during respiratory inspiration. In animal studies, normobaric oxygen therapy was shown to nonlinearly increase penumbral partial pressure of oxygen, maintaining physiological levels during middle cerebral artery occlusion when inspiratory oxygen fraction was at least 0.95.[8] Accordingly, in a randomized pilot trial, oxygen at 45 liters per minute via a simple face mask led to significant arterial hyperoxygenation, temporary NIHSS improvement, and stabilization of diffusion-weighted lesions on MRI during normobaric oxygen therapy.[9] Compared to hyperbaric oxygen therapy, which may provide superior brain protection according to animal studies, normobaric oxygen therapy is inexpensive, widely available and easy to administer during acute stroke workup including mechanical thrombectomy.[5]

(2) We aimed to **initiate normobaric oxygen therapy early**. Brain tissue oxygen is depleted within seconds after blood flow interruption,[1] and animal studies have shown no neuroprotection with delayed normobaric oxygen therapy.[10] Considering results from extended time window mechanical thrombectomy trials, the high ASPECTS required for enrollment into PROOF combined with the time window of 6 hours after symptom onset/notice would sufficiently well indicate relevant volumes of potentially salvageable penumbra.[11]

(3) As a proof of concept, we focused on mechanical thrombectomy candidates as our study population. In animal models, normobaric oxygen therapy only consistently led to infarct volume reduction when **ischemia was temporary** and lasted up to three hours.[4] Given that "nothing can hold its breath forever" beneficial effects of normobaric oxygen therapy vanished in case of no recanalization.[9] mechanical thrombectomy provides high rates of successful reperfusion, and clearly defined ischemia duration and revascularization status.[3,12]

(4) We aimed to **stop normobaric oxygen therapy at the end of mechanical thrombectomy procedure**. Few animal studies evaluated post-reperfusion normobaric oxygen therapy and reported mixed results.[8,13,14] While Liu et al. warned that over-oxygenation during reperfusion could potentially lead to free radical toxicity, they also pointed out that hyperoxia seems more tolerable to the brain than hypoxia.[8] This is why we did not stop normobaric oxygen therapy immediately after successful reperfusion, but allowed NBO to also cover treatment of accidental new ischemia in case of thrombus dislocation during clot retrieval.

9 Methodology

Study design: prospective, multicenter, adaptive, parallel group, randomized (1:1), standard treatment-controlled, open-label, clinical trial with blinded outcome assessment (PROBE design).

Patients were randomized (1:1) using the minimization method with preferred treatment probability of 0.9 via the www.randomizer.at platform with following strata: (1) baseline brain imaging modality, (2) side of LVO, (3) LVO location, (4) baseline NIHSS, (5) time window, and (6) study site.

10 Number of Patients

From 17.08.2019 to 13.05.2022, 223 of the initially planned 460 patients were enrolled in the PROOF study.

11 Main Inclusion Criteria

Subjects meeting all of the following criteria had been considered for admission to the trial:

- age ≥ 18 years
- acute terminal internal carotid artery, M1 and/or M2/3 segment(s) occlusion on CT/MR angiography
- likely mechanical thrombectomy
- NIHSS ≥ 6
- ASPECTS 6–10 on non-contrast CT or 5–10 on diffusion-weighted MRI
- CT/MR perfusion prior to normobaric oxygen therapy
- Normobaric oxygen therapy can be initiated within 6 hours of symptom onset or notice in case of unknown onset, and within 30 minutes after baseline brain imaging
- pre-stroke modified Rankin Scale score 0–2
- breastfeeding women must stop breastfeeding (not applicable in Switzerland)
- deferred consent or consent by patient/legally authorized representative (see study protocol Section 14.5 Subject Information and Informed Consent)

12 Test investigational medicinal product

For normobaric oxygen therapy, oxygen for medical use (ATC code: V03AN01) at 1 atmosphere was administered at ≥ 40 liters per minute via a non-rebreather face-mask with reservoir or, if ventilated, 1.0 inspiratory oxygen fraction. Medical oxygen was taken from either oxygen cylinders or wall socket. Batch numbers are not applicable in this trial.

13 Duration of treatment

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 thrombectomy, or for 4 hours, if mechanical thrombectomy was not attempted or stopped prior to manipulation of intracranial anterior circulation large vessel occlusion.

14 Reference therapy

Control arm: oxygen supplementation if oxygen saturation ≤ 94% at 2 to 4 L/min via nasal cannula according to guidelines of the European Stroke Organisation, or in case of mechanical thrombectomy-related ventilation, ventilation with an initial inspiratory oxygen fraction of 0.3 to be gradually increased if oxygen saturation ≤ 94%.

15 Criteria for evaluation

15.1 Efficacy

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).

Secondary outcomes
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 during mechanical thrombectomy (or at 90 minutes), relative percent change in ischemic core volume from baseline to 24 hours, and Barthel Index, Montreal Cognitive Assessment, Montgomery-Åsberg Depression Rating Scale, and the patient reported outcomes Stroke Impact Scale-16 and EuroQoL-5 Dimensions-5 Levels at 90 days.

Exploratory outcomes are imaging and blood biomarkers.

15.2 Safety

Safety outcomes include vasospasm during mechanical thrombectomy, intracranial hemorrhage at 24 hours, symptomatic intracranial hemorrhage until day 5, respiratory adverse events, and all serious adverse events until day 90.

16 Statistical methods

Patients were randomized to a treatment arm in a 1:1 ratio. The randomization procedure was provided by a web-based with study-specific roles assigned to study personnel. It ensured allocation concealment in that it required the entry of the stratification parameters before disclosing the result of the assignment.
Minimization [was used to consider several strata when allocating treatment. These were:

- Brain imaging modality at baseline (CT vs. MRI)
- Side of intracranial large vessel occlusion (left vs. right)
- Intracranial large vessel occlusion location (terminal internal carotid artery with involvement of the M1-segment of the middle cerebral artery/carotid-T vs. proximal M1-segment vs. distal M1-segment (distal of perforating branches) vs. M2/3-segment(s)
- NIHSS at baseline: 6-10, 11-20, 21 and more
- Time window known ‹ 6h vs. unknown/wake-up
- Study site

Staff that was involved in the emergency treatment of patients was not blinded to the treatment allocation as blinding would only have been possible by comparing normobaric oxygen therapy to high-flow air, which does not represent standard stroke treatment and, by itself, is known to exert clinically relevant effects on respiration and ventilation. Outcome-raters at the image core laboratory (i.e., Eppdata) were blinded to the respective treatment as they did not receive any information about randomization and the prior clinical course.

All analyses were specified in a statistical analysis plan (SAP). The SAP was updated after the interim analyses took place.

Disposition, baseline characteristics and medical history were analyzed descriptively.

The primary analysis was performed for the full analysis set (FAS) which comprises all patients randomized into the trial of whom data may be used (valid informed consent) and who are ≥ 18 years. In this set, every patient is analyzed according to the group randomized into, following an intention-to-treat approach.
The FAS was used for the analysis of primary and secondary efficacy and safety outcomes.

The primary outcome was the ischemic core growth from baseline to 24 hours (Visit 5), i.e., ischemic core volume at baseline subtracted from the infarct volume at Visit 5. The FAS was used to assess the primary outcome. The actual volume was derived by Core Image Lab (Eppdata) according to study protocol section 10.4 Brain imaging acquisition assessment (see also SAP PROOF V04 Annex Core Volume Definition 13.04.2022).

Missing values were replaced for the baseline ischemic core volume using single imputation. Imputation as linear regression of ischemic core volume at baseline given brain imaging modality at baseline (CT vs MR), occlusion side at baseline (left vs. right) and occlusion location at baseline (terminal internal carotid artery (ICA) with involvement of the M1 segment of the middle cerebral artery/carotid-T vs. proximal M1 segment vs. distal M1 segment vs. M2/M3 segments), tandem stenosis (yes vs. no/unknown) at baseline, NIHSS at baseline (continuous), ASPECTS at baseline as reported by Core Image Lab (EppData) if available otherwise as documented in the eCRF. In case of doubt (including missing or unknown information), a medical expert assessed the explanatory variables. The linear regression predictor was substituted for the missing value.

Missing values were planned to be replaced for the primary outcome using single imputation if the number of missing values is less than 10%, otherwise multiple imputation should be used. Imputation as linear regression of infarct volume at Visit 5 given baseline ischemic core volume. If single imputation was used, the linear regression predictor would be substituted for the missing value.

To analyze the primary hypothesis a rerandomization test was used considering the strata. One interim analysis was prespecified after 160 patients were enrolled and treated. The interim analysis was restricted to the first 160 randomized patients. The test was performed at a one-sided level of α_1=0.0233. If the null hypothesis of no impeding effect of normobaric oxygen therapy on core volume could not be rejected at this level but could be rejected at the α_0=.5 level, the trial was planned to be continued. If it could not be rejected at α_0=.5, the trial would be stopped for futility. If it could be rejected at α_1, it would be stopped for efficacy. In case the trial would have continued, the α_2 level would have been used for the planning of the rest of the trial and would have been set to c_α/p, where c_α = 0.0087 and p being the p-value of the test used in the interim analysis, with a power of 65 per cent, in order to maintain the total level of α = .05 and an overall power of 80 per cent.

As sensitivity analysis, the primary analysis was repeated using a loner mixed model considering the following variables ("standard set"):

- baseline volume of ischemic core
- tandem stenosis (yes vs. no/unknown)
- Stratification variables:
    - Brain imaging modality at baseline (CT vs MR)
    - Large vessel occlusion side (left vs. right)
    - Large vessel occlusion location (terminal internal carotid artery vs. proximal M1 vs. distal M1 vs. M2/M3)
    - NIHSS at baseline (here continuous instead of categorical as originally planned in the protocol)
    - study site (as a random effect)
    - time window from symptom onset to randomization ‹ 6 h vs. unknown/wake up/≥6h

The change of NIHSS score was calculated as difference between the respective visit and baseline and was tabulated by visit against treatment group, using number of non-missing values, minimum, median, maximum, mean and standard deviation.
The change of NIHSS score was calculated as difference between 24 h visit and baseline will used as response variable in a linear mixed regression model with the standard set of variables (as reported by Core Image Lab (Eppdata) (if available) otherwise as documented in the CRF) as explanatory variables. Parameter estimates were listed with estimate, standard error, p-value, 95 per cent confidence interval.

Adverse events (AEs) were collected from the first administration of normobaric oxygen therapy/standard therapy for up to the last study visit.
AE were coded using MedDRA. They were tabulated against treatment group by SOC and PT using number of events and relative and absolute frequency of patients. Serious AE and AEs of special interest were tabulated against treatment group.
In addition, to the interim analyses where futility and efficacy were evaluated, DSMB meetings were planned to evaluate the safety.

For further analyses, see SAP Versiont 5.
All analyses except for the primary analysis were conducted using SAS 9.4. R was used for the primary analysis.

Sample size estimates
We planned adaptive sample size with interim analysis as the effect of NBO on infarct volume is unknown. Sample size calculation was based on absolute core growth of 62 anterior-circulation LVO cases from SWIFT-PRIME who underwent MT and achieved successful reperfusion.[12] Mean and standard deviation were estimated as 17.8 ±21.4 mL from the quartiles, assuming normal distribution.[12] We expected a 50% reduction of core growth (i.e., 8.9 mL) in those 75% of NBO-treated participants who would undergo MT (93.75% of all cases) and achieve successful reperfusion (80% of MT cases[3,12]). Considering the other 25% of failed/not attempted MT would reduce the mean effect to 6.68 mL. Consequently, 138 participants per arm would be needed for a one-sided test at alpha 0.05 to detect a treatment effect with 80% power. Adaptive design[15] allowed the trial to be stopped for success (p <0.0233) or futility (p ≥0.5) after interim analysis (80 patients per arm), or to be continued with additional 11 to 148 patients per arm.

17 Summary/Conclusions

17.1 Disposition/ Baseline Characteristics/Medical history

223 patients were randomized. 28 patients could not complete the study due to death, 3 patients were lost to follow-up, 1 patient withdrew the informed consent, 1 patient was not compliant/stopped due to medical reasons, 6 patients stopped the study earlier due to other reasons.
56% of the patients were 65 to <85 years old. 51% of the patients were male.
87% of the patients had at least one prior or concomitant disease. 65% of the patients had a history of arterial hypertension.

17.2 Efficacy Results

Interim Analysis: A mean core growth of about 41 mL was observed in the treatment arm compared to 21 mL in the control arm. Moreover, the median and 75th percentile also favour the control arm (16 vs 5 mL for the median and 53 vs 22 mL for the 75th percentile). The mean difference between arms was found to be about 21 mL more core growth in the treatment arm and the one-sided re-randomization p-value of p≈0.95 was greater than 0.5, which was equivalent to saying that the “direction of the effect for the primary outcome favored the control arm”. A sensitivity analysis confirmed this result as do subgroups defined by time of known onset of the stroke or of recognition of first symptoms.
The clinical outcome NIHSS after 24h was very similar between the two arms and the point estimate also favored the control arm (reduction by 5.1 points in the control arm vs 4.1 points in the intervention arm).
Therefore, the recruitment was stopped due to futility.

Final Analysis: Further 63 patients were recruited. Therefore, the analysis of the primary outcome was evaluated as intended if no stop due to futility would have taken place, i.e., the analysis was conducted for the 63 patients in the same way the first 160 randomized patients had been analyzed. The mean difference between arms was found to be about 18 mL less core growth in the treatment arm and the one-sided re-randomization p-value of p≈0.226, but the alpha for the 2nd stage is $c_{alpha}/p1 = 0.0091821$.
As sensitivity analysis all patients were analyzed using a linear mixed model showing a similar result as in the interim analysis. The same was valid for the NIHSS.

17.3 Safety Results

Interim Analysis: There were 11 (14%) deaths in the intervention arm and 8 (10%) in the control arm. In addition, the total AE analysis also suggests that the groups are similar and with a slight advantage in the control arm (84% of intervention patients had an AE vs 72% of control patients and for SAEs it was 42% vs 38%). The same picture emerges for AEs of special interest (14% of intervention patients vs 11% of control patients).

Final Analysis: Similar results as in the interim analyses were achieved in analyzing all 223 patients.

17.4 Conclusion

Despite implementing insight from animal models in which normobaric oxygen therapy was shown beneficial (i.e., (1) near 100% oxygen was (2) initiated early in (3) short temporary ischemia and (4) stopped soon after reperfusion), NBHO was not superior to standard oxygen in preventing ischemic core growth in PROOF patients with acute anterior circulation stroke due to proximal intracranial vessel occlusion who underwent endovascular mechanical thrombectomy in most cases.

We could not replicate the strong beneficial effects of normobaric oxygen therapy in our total cohort that were achieved in two recent Chinese single center studies. With one study being similar to PROOF,[16] the other, however, started normobaric oxygen therapy only after successful endovascular mechanical thrombectomy.[17]

Importantly, our findings however, did not reveal safety concerns neither with regard to intracranial hemorrhagic complications nor to respiratory, cardiovascular or other adverse events.

We assume reasons for failure to be heterogeneous. We will carefully explore possible reasons in order not to condemn normobaric oxygen therapy inappropriately, considering its strong effects in animal models in “freezing the penumbra”.

18 Appendices

18.1 References

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18.2 Tables

Table 18.2.1: Disposition

Category	Subcategory	NBHO	Control	Total
Randomization		112	111	223
Included in interim analysis		80	80	160
End of study	Regular completion	93	91	184
	Death	14	14	28
	Medical reasons/non compliance		1	1
	Withdrawl	1		1
	Lost-to-follow-up	1	2	3
	Other	3	3	6

Table 18.2.2: Baseline Characteristics

Parameter		NBHO (N=112)		Control (N=111)		Total (N=223)	
		#	%	#	%	#	%
Age	n	112	100.0	111	100.0	223	100.0
	>=18 -< 65 years	30	26.8	30	27.0	60	26.9
	>=65 -< 85 years	64	57.1	61	55.0	125	56.1
	>=85 years	18	16.1	20	18.0	38	17.0
Sex	n	112	100.0	111	100.0	223	100.0
	Female	55	49.1	55	49.5	110	49.3
	Male	57	50.9	56	50.5	113	50.7
Brain Imaging Method	n	112	100.0	111	100.0	223	100.0
	MRI	11	9.8	9	8.1	20	9.0
	CT	101	90.2	102	91.9	203	91.0
Side of LVO	n	112	100.0	111	100.0	223	100.0
	Left	60	53.6	58	52.3	118	52.9
	Right	52	46.4	53	47.7	105	47.1
LVO location	n	112	100.0	111	100.0	223	100.0
	Terminal internal carotid artery (ICA) with involvement of the M1-segment of the middle cerebral artery (MCA)/ carotid-T	19	17.0	13	11.7	32	14.3
	Proximal M1-segment	40	35.7	41	36.9	81	36.3
	Distal M1-segment (distal of perforating branches)	27	24.1	28	25.2	55	24.7
	M2/M3 segment(s)	26	23.2	29	26.1	55	24.7

Time window until randomization	n	112	100.0	111	100.0	223	100.0
	known, < 6 h	95	84.8	86	77.5	181	81.2
	unknown/wake up/>= 6 h	17	15.2	25	22.5	42	18.8
NIH Stroke Scale Score	n	112	100.0	111	100.0	223	100.0
	5 and less			1	0.9	1	0.4
	6-10	33	29.5	31	27.9	64	28.7
	11-20	63	56.3	66	59.5	129	57.8
	21 and more	16	14.3	13	11.7	29	13.0
Tandem stenosis	n	112	100.0	111	100.0	223	100.0
	Yes	18	16.1	13	11.7	31	13.9
	No	94	83.9	98	88.3	192	86.1
Stroke Subtype Classification (TOAST)	n	110	100.0	107	100.0	217	100.0
	1-Large-artery atherosclerosis (embolus/thrombosis)	13	11.8	18	16.8	31	14.3
	2-Cardioembolism (high-risk/ medium-risk)	59	53.6	63	58.9	122	56.2
	4-Stroke of other determined etiology	8	7.3	2	1.9	10	4.6
	5a-Stroke of undetermined etiology - Two or more causes identified	2	1.8	3	2.8	5	2.3
	5b-Stroke of undetermined etiology – Negative evaluation	20	18.2	16	15.0	36	16.6
	5c-Stroke of undetermined etiology – Incomplete evaluation	8	7.3	5	4.7	13	6.0

n is the number of patients in the Full Analysis Set with non-missing values. # - number of patients, % percentage of patients bases on n

Table 18.2.3: Medical History/Prior and Concomitant medication

	NBHO (N=112)	Control (N=111)	Total (N=223)
At least one prior disease reported	380 / 93 (83.0%)	445 / 101 (91.0%)	825 / 194 (87.0%)
At least one prior medication taken	366 / 78 (69.6%)	542 / 84 (75.7%)	908 / 162 (72.6%)
At least one concomitant medication taken	2093 / 111 (99.1%)	2013 / 108 (97.3%)	4106 / 219 (98.2%)

x / y (z.z%): x = Number of events/drugs taken, y = Number of patients with events/drugs taken, z.z = Percentage of patients with events/drugs taken
Percentages are based on the number of patients in the Full Analysis Set.

Table 18.2.4: Core Volume/NHISS – Descriptively

Core Volume (mL)

Analysis	Arm	Visit	n	Mean	Standard deviation	Minimum	25%-Quantile	Median	75%-Quantile	Maximum
Interim analysis	NBHO (N=80)	Screening	80	21.37	30.06	0	0.5	10.00	27.9	132
		24h-Follow up	79	62.39	84.81	0	5.96	28.90	65.46	339.99
		Change	79	41.19	75.47	-75.34	0	15.55	52.55	276.55
	Control (N=80)	Screening	79	22.57	33.03	**0**	**0**	10.00	30	147
		24h-Follow up	80	43.22	73.41	**0**	6.3	15.30	35.7	421.7
		Change	79	21.03	70.67	-130.72	-7	5.32	22.15	275.7
Final analy-sis	NBHO (N=112)	Screening	106	25.13	40.28	0.00	2.00	13.00	30.00	322.00
		24h-Follow up	109	54.76	77.23	0.00	4.50	23.27	63.33	339.99
		Change	105	30.73	77.73	-316.34	-2.57	8.46	49.75	276.55
	Control (N=111)	Screening	110	20.94	30.07	0.00	0.00	9.00	27.00	147.00
		24h-Follow up	110	41.63	73.48	0.00	3.60	14.40	36.42	421.70
		Change	109	20.59	69.78	-130.72	-7.28	4.12	21.49	332.80

n is the number of patients in the Full Analysis Set with non-missing screening values and/or non-missing follow-up values.

NIHSS

Analysis	Arm	Visit	n	Mean	Standard deviation	Minimum	25%-Quantile	Median	75%-Quantile	Maximum
Interim analysis	NBHO (N=80)	Screening	80	14.88	4.94	6	10	15.00	19	24
		Visit 5	79	10.73	10.26	0	2	7.00	19	38
		Change	79	-4.13	9.07	-19	-11	-6.00	1	25
	Control (N=80)	Screening	80	14.08	5.34	5	10	15.00	17.5	30
		Visit 5	79	8.91	8.08	0	2	7.00	13	37
		Change	79	-5.14	7.53	-23	-9	-6.00	-1	18
Final analy-sis	NBHO (N=112)	Screening	112	14.75	5.09	6.00	10.00	15.00	19.00	26.00
		Visit 5	111	9.66	9.72	0.00	2.00	6.00	17.00	38.00
		Change	111	-5.08	8.88	-24.00	-11.00	-7.00	0.00	25.00
	Control (N=111)	Screening	111	14.39	5.27	5.00	10.00	15.00	18.00	30.00
		Visit 5	111	8.61	8.09	0.00	2.00	6.00	13.00	37.00
		Change	111	-5.77	7.54	-23.00	-10.00	-6.00	-2.00	18.00

n is the number of patients in the Full Analysis Set with non-missing screening values and/or non-missing follow-up values.

Table 18.2.5: Core Volume – Primary Analysis

Analysis	Arm	n	Mean Change	Standard deviation	Difference of mean changes	Standard error	p-value
Interim analysis	NBHO	80	41.06	74.996	20.46	11.495	0.9475
	Control	80	20.60	70.332	Ref		Ref
Final analysis	NBHO	32	2.65	69.71	-17.65	17.24	0.226
	Control	31	20.29	67.13	Ref		Ref

The analysis is based on the full analysis set. Missing values were replaced for the baseline core volume using single imputation. Imputation was conducted as linear regression for ischaemic core volume at baseline given brain imaging modality at baseline (CT vs MR), occlusion side at baseline (left vs. right), occlusion location at baseline (terminal internal carotid artery (ICA) with involvement of the M1 segment of the middle cerebral artery (MCA)/carotid-T vs. proximal M1 segment vs. distal M1 segment vs. M2/M3 segments), tandem stenosis (yes vs. no/unknown) at baseline, NIHSS at baseline (continuous) and ASPECTS at baseline as reported by CoreLab if available otherwise as documented in the eCRF. In case of doubt (including missing or unknown information), a medical expert will assess the explanatory variables. The linear regression predictor was substituted for the missing value. Missing values were replaced for the primary endpoint using single imputation. Imputation was conducted as linear regression for ischaemic core volume at 24 hours given baseline core volume. The linear regression predictor was substituted for the missing value. In case of death, ischemic core growth was set to max. individual ischemic core growth (provided by the CoreLab according to the study protocol) for a timepoint preceded by patient's death.
A re-randomization test was performed where the same observations with the same randomization criteria will undergo the same randomization algorithm leading to different treatment allocations than in the study. The strata from the randomization were used. Erroneously selected strata immediately recognized were corrected in the randomization tool.
The alpha for the 2nd stage is 0.0087/0.9475 = 0.0091821.

Table 18.2.6: Core Volume/NIHSS – Regression

Core Volume (mL)

Analysis	Arm	n	Estimate	Standard error	p-value (two-sided)	95%-Confidence interval	
						Lower	Upper
Interim analysis	Control vs NBHO (Ref)	160	-13.0394	11.5100	0.2593	-35.8042	9.7253
Final analysis	Control vs NBHO (Ref)	223	-8.4747	9.3452	0.3656	-26.9053	9.9560

The analysis is based on the full analysis set. The same replacements as for the primary analysis were used for missing values.
Linear mixed regression with change from screening as dependent variable was conducted using the following explanatory variables:

- baseline volume of ischaemic core
- brain imaging modality at baseline (CT vs MR)
- occlusion side (left vs. right)
- NIHSS at baseline (continuous)
- occlusion location (terminal internal carotid artery (ICA) with involvement of the M1 segment of the middle cerebral artery (MCA)/carotid-T vs. proximal M1 segment vs. distal M1 segment vs. M2/M3 segments)
- tandem stenosis (yes vs no/unknown)
- study site (as a random effect)
- time window from onset of symptoms <6h vs unknown/wake up/>=6h.

NHISS – Visit 5

Analysis	Arm	n	Estimate	Standard error	p-value (two-sided)	95%-Confidence interval	
						Lower	Upper
Final analysis	Control vs NBHO (Ref)	222	-0.5295	1.0599	0.6179	-2.6198	1.5608

The analysis is based on the full analysis set.
Linear mixed regression with change from screening as dependent variable was conducted using the following explanatory variables:
• baseline volume of ischaemic core
• brain imaging modality at baseline (CT vs MR)
• occlusion side (left vs. right)
• NIHSS at baseline (continuous)
• occlusion location (terminal internal carotid artery (ICA) with involvement of the M1 segment of the middle cerebral artery (MCA)/carotid-T vs. proximal M1 segment vs. distal M1 segment vs. M2/M3 segments)
• tandem stenosis (yes vs no/unknown)
• study site (as a random effect)
• time window from onset of symptoms <6h vs unknown/wake up/>=6h.
• Baseline NHISS value.

Table 18.2.7 – Adverse Events Overview

Analysis	Category	NBHO	Control
Interim Analysis*	At Least One Adverse Event	244 / 68 (84.0%)	235 / 57 (72.2%)
	At Least One Serious Adverse Event	54 / 34 (42.0%)	38 / 30 (38.0%)
	At Least One Adverse Event Event of Special Interest	12 / 11 (13.6%)	10 / 9 (11.4%)
	At Least One Fatal Adverse Event	13 / 11 (13.6%)	9 / 8 (10.1%)
Final Analysis**	At Least One Adverse Event	306 / 90 (80.4%)	293 / 78 (70.3%)
	At Least One Serious Adverse Event	91 / 48 (42.9%)	66 / 44 (39.6%)
	At Least One Adverse Event Event of Special Interest	19 / 18 (16.1%)	13 / 11 (9.9%)
	At Least One Fatal Adverse Event	17 / 15 (13.4%)	20 / 15 (13.5%)
	At Least One Respiratory Adverse Event	23 / 19 (17.0%)	17 / 14 (12.6%)
	At Least One Myocardial Infarction	5 / 5 (4.5%)	19 / 15 (13.5%)
	At Least One MACE	42 / 33 (29.5%)	57 / 42 (37.8%)
	At Least One Pneumonia	18 / 17 (15.2%)	17 / 16 (14.4%)
	At Least One Decompressive Hemicraniectomy	3 / 2 (1.8%)	2 / 1 (0.9%)
	At Least One Symptomatic ICH According to ECASIII	4 / 4 (3.6%)	4 / 3 (2.7%)
	At Least One Symptomatic ICH According to HDBC	6 / 5 (4.5%)	4 / 3 (2.7%)

x / y (z.z%): x = Number of events, y = Number of patients with events, z.z = Percentage of patients with events
Percentages are based on the number of patients in the Full Analysis Set.
* For the interim analysis actual arms were used defined by a medical expert: NBHO: N=81, Control: N=79
** For the final analysis the planned arm was used: NBHO: N=112, Control: N=111

Table 18.2.8 – Adverse Events Assessed By CoreLab

		NBHO (N= 112)		Control (N= 111)	
		#	%	#	%
Malignant brain edema	n	156	100.0	173	100.0
	No	150	96.2	169	97.7
	Yes	6	3.8	4	2.3
New microbleeds on 24-hour follow-up MRI vs. Baseline T2*	n	14	100.0	13	100.0
	No	13	92.9	13	100.0
	Yes	1	7.1		
Occurrence of embolization***	n	165	100.0	155	100.0
	No	162	98.2	151	97.4
	Yes	3	1.8	4	2.6
Occurrence of intracranial vessel perforation**	n	104	100.0	96	100.0
	No	104	100.0	96	100.0
Occurrence of vasospasms	n	104	100.0	96	100.0
	No	80	76.9	74	77.1
	Yes	24	23.1	22	22.9
Occurrence of vasospasms in final DSA run	n	104	100.0	96	100.0
	No	87	83.7	82	85.4
	Yes	17	16.3	14	14.6

n is the number of patients in the Full Analysis Set with non-missing values.
- number of patients, % percentage of patients bases on n
** at the any time of the procedure, *** in previously uninvolved (or new) territories (ENT) as seen on the final control angiogram at the end of the procedure