Clinical trial results:
Hyperbaric Oxygen for Treatment of Long COVID syndrome; A Randomized, Placebo-Controlled, Double-Blind, Phase II Clinical Trial

Summary

EudraCT number	2021-000764-30
Trial protocol	SE
Global end of trial date	17 June 2024

Results information

Result version number	v1 (current)
This version publication date	01 November 2025
First version publication date	01 November 2025

Trial information

Trial identification

Sponsor protocol code	HOT-LOCO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04842448
WHO universal trial number (UTN)	-
Other trial identifiers	Karolinska University hospital: K2021-1592, Karolinska Institutet: 4-621/2021

Notes:

Sponsors

Sponsor organisation name	Karolinska University Hospital
Sponsor organisation address	Eugeniavägen 3, Stockholm, Sweden, 17176
Public contact	Hyperbaric unit F3:76, Karolinska University Hospital, +46 8123 946 80, anders.kjellberg@regionstockholm.se
Scientific contact	Hyperbaric unit F3:76, Karolinska University Hospital, +46 8123 946 80, anders.kjellberg@regionstockholm.se

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	17 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2024
Global end of trial reached?	Yes
Global end of trial date	17 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if HBOT improves HRQoL (role limitations due to physical health and physical functioning) for patients with Long COVID compared to placebo (sham treatment).

Protection of trial subjects:

Blood sampling may have negative impact on the subject as a large number of samples will be necessary for the clinical investigation and may be needed for other trials and therefore blood tests already collected were used as much as possible.

The study was conducted in compliance with the protocol, regulatory requirements, Good Clinical Practice (GCP) and ethical principled of the latest version of the Declaration of Helsinki as adopted by the World medical Association.

Background therapy:

Medications and treatments that were considered “best practice”was given to the subjects at the discretion of their attending physician/physiotherapist/phycologist. Subjects was discouraged to try new medications, treatments or remedies that were not evidence based during the course of the trial.

Evidence for comparator:

The placebo protocol is previously well established and even experienced divers cannot differ between “sham treatment” and HBO2.

Actual start date of recruitment	20 September 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	80
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between Sept 15, 2021, and June 20, 2023, 80 subjects (65 women, 15 men) were enrolled (40 in each group). 80 subjects were randomized.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	129[1]
Intermediate milestone: Number of subjects	Signed informed consent: 90
Intermediate milestone: Number of subjects	Screening visit 1: 83
Number of subjects completed	80

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion criteria: 3
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Declined participation: 6
Reason: Number of subjects	Exclusion criteria: 5
Reason: Number of subjects	Inclusion-/exclusion criteria: 13
Reason: Number of subjects	No response to written information: 20

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to have started the pre-assignment period (129 subjects) are all subjects that were pre-screened. The number of enrolled subjects are those that were found to eligible for inclusion and randomisation (80 subjects).

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, Subject

Blinding implementation details:

Subjects and all study personell that participate in the asessement of sympoms and objective findings were blinded to the treatment. The placebo protocol is well established and even experienced divers cannot differ between "sham treatment" and HBO2 (Lansdorp and van Hulst, 2018). Pressure gauges that could seen by subjects were covered during the treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	HBO2

Arm description:

Hyperbaric Oxygen Therapy/Treatment

Arm type	Experimental

Investigational medicinal product name	Conoxia
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, cryogenic
Routes of administration	Inhalation use

Dosage and administration details:

Hyperbaric oxygen 240 kPa for 90 minutes (with 10 min compression time, two air breakes and 10 minutes decompression time). The number and frequency of treatments and timing depended on the subject´s tolerance and available resources at the discretion of the
attending physician, but the recommended interval was 2–5 treatments per week with a maximum of 10 treatments within 6 weeks from randomization. To satisfy the treatment compliance, a subject needed to complete at least 5 treatments.

Arm title	Placebo

Arm description:

Placebo Air, compressed air medical grade

Arm type	Placebo
Investigational medicinal product name	Medicinal gas, compressed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

Sham treatment with medical air was administered by increasing pressure to 1·34 ATA and then reduced to 1·2 ATA for 90 min with two five min air breaks (re-breather mask).

Number of subjects in period 1	HBO2	Placebo
Started	40	40
Completed	37	32
Not completed	3	8
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	1
Transferred to other arm/group	1	-
Lost to follow-up	-	3
Missing data	1	3

Baseline characteristics

Reporting groups	
Reporting group title	HBO2
Reporting group description:	
Hyperbaric Oxygen Therapy/Treatment	
Reporting group title	Placebo
Reporting group description:	
Placebo Air, compressed air medical grade	

Reporting group values	HBO2	Placebo	Total
Number of subjects	40	40	80
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	41.1	41.4	
standard deviation	± 10.14	± 8.16	-
Gender categorical			
Units: Subjects			
Female	32	33	65
Male	8	7	15
Tobacco, smoking			
Units: Subjects			
Never smoker	28	31	59
Ex-smoker	12	9	21
Tobacco, smokeless			
Units: Subjects			
Never used Swedish snus	32	34	66
Ex-user Swedish snus	2	5	7
Casual user Swedish snus	2	0	2
Daily user Swedish snus	4	0	4
Not recorded	0	1	1
Full time work/Study before COVID-19			
Units: Subjects			
Yes	40	35	75
No	0	5	5
Full time work/Study at baseline			

Units: Subjects			
Yes	4	5	9
No	36	35	71
Education (Diploma/University degree) Units: Subjects			
Yes	31	34	65
No	9	6	15
Fully vaccinated Units: Subjects			
Yes	29	26	55
No	11	14	25
Positive SARS-CoV-2 PCR Units: Subjects			
Yes	16	14	30
No	24	26	50
Positive SARS-CoV-2 antibodies Units: Subjects			
Yes	23	18	41
No	17	22	39
Body mass index (BMI) Units: kilogram(s)/square metre			
arithmetic mean	24.4	24.3	
standard deviation	± 4.12	± 4.13	-
Physical activity, exercise (min/week) Units: minute			
arithmetic mean	23.5	14.3	
standard deviation	± 54.6	± 30.8	-
Time from COVID-19 onset Units: month			
arithmetic mean	26.2	25.1	
standard deviation	± 7.1	± 8.7	-
RAND-36 domain Physical functioning (PF) Units: points			
arithmetic mean	39.8	37.9	
standard deviation	± 18.6	± 19.0	-
RAND-36 domain Role-functioning physical (RP) Units: points			
arithmetic mean	0.6	0.0	
standard deviation	± 4.0	± 0.0	-
RAND-36 domain General health (GH) Units: points			
arithmetic mean	28.8	25.0	
standard deviation	± 14.0	± 11.0	-
RAND-36 domain Mental health (MH) Units: points			
arithmetic mean	61.1	60.0	
standard deviation	± 16.6	± 16.5	-
RAND-36 domain Role emotional (RE) Units: points			
arithmetic mean	65.0	58.4	

standard deviation	± 45.3	± 45.2	-
RANd-36 domain Social functioning (SF)			
Units: points			
arithmetic mean	21.4	22.4	
standard deviation	± 22.5	± 20.5	-
RAND-36 domain Body pain (BP)			
Units: points			
arithmetic mean	51.6	51.6	
standard deviation	± 26.4	± 24.9	-
RAND-36 domain Vitality (VT)			
Units: points			
arithmetic mean	19.1	14.8	
standard deviation	± 19.1	± 12.1	-
EQ-5D (VAS)			
Units: points			
arithmetic mean	38.4	39.5	
standard deviation	± 15.1	± 16.8	-
EQ-5D-5L (index)			
Units: points			
arithmetic mean	0.5	0.5	
standard deviation	± 0.2	± 0.2	-
Reactive hyperemia index (RHI)			
Units: points			
arithmetic mean	2.1	2.0	
standard deviation	± 0.6	± 0.6	-
Cardiac Index (Nexfin)			
Units: L/min/m2			
arithmetic mean	3.14	3.2	
standard deviation	± 0.84	± 0.76	-
Chair standing test (CST 30s)			
Units: No/30s			
arithmetic mean	12.1	11.0	
standard deviation	± 4.4	± 4.1	-
6 minute walk test (6MWT)			
Units: metre			
arithmetic mean	468.8	449.7	
standard deviation	± 129.6	± 141.8	-

Subject analysis sets

Subject analysis set title	FAS analysis
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) population includes all randomized subjects who were exposed at least once to the study intervention. FAS subjects were analysed according to their randomised/assigned treatment irrespective of which treatment they actually received.

Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety (SAF) population includes all randomized subjects that have received at least one study treatment. SAF patients were analysed according to their actual treatment received.

Reporting group values	FAS analysis	Safety analysis	
Number of subjects	80	80	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	41.3	41.3	
standard deviation	± 9.15	± 9.15	
Gender categorical Units: Subjects			
Female	65	65	
Male	15	15	
Tobacco, smoking Units: Subjects			
Never smoker	59	59	
Ex-smoker	21	21	
Tobacco, smokeless Units: Subjects			
Never used Swedish snus	66	66	
Ex-user Swedish snus	7	7	
Casual user Swedish snus	2	2	
Daily user Swedish snus	4	4	
Not recorded	1	1	
Full time work/Study before COVID-19 Units: Subjects			
Yes	75	75	
No	5	5	
Full time work/Study at baseline Units: Subjects			
Yes	9	9	
No	71	71	
Education (Diploma/University degree) Units: Subjects			
Yes	65	65	
No	15	15	
Fully vaccinated Units: Subjects			
Yes	55	55	
No	25	25	
Positive SARS-CoV-2 PCR Units: Subjects			

Yes	30	30	
No	50	50	
Positive SARS-CoV-2 antibodies			
Units: Subjects			
Yes	41	41	
No	39	39	
Body mass index (BMI)			
Units: kilogram(s)/square metre			
arithmetic mean	24.4	24.4	
standard deviation	± 4.10	± 4.10	
Physical activity, exercise (min/week)			
Units: minute			
arithmetic mean	18.9	18.9	
standard deviation	± 44.3	± 44.3	
Time from COVID-19 onset			
Units: month			
arithmetic mean	25.6	25.6	
standard deviation	± 7.9	± 7.9	
RAND-36 domain Physical functioning (PF)			
Units: points			
arithmetic mean	38.8	38.8	
standard deviation	± 18.7	± 18.7	
RAND-36 domain Role-functioning physical (RP)			
Units: points			
arithmetic mean	0.3	0.3	
standard deviation	± 2.8	± 2.8	
RAND-36 domain General health (GH)			
Units: points			
arithmetic mean	25.0	25.0	
standard deviation	± 11.0	± 11.0	
RAND-36 domain Mental health (MH)			
Units: points			
arithmetic mean	60.6	60.6	
standard deviation	± 16.5	± 16.5	
RAND-36 domain Role emotional (RE)			
Units: points			
arithmetic mean	61.7	61.7	
standard deviation	± 45.1	± 45.1	
RANd-36 domain Social functioning (SF)			
Units: points			
arithmetic mean	21.9	21.9	
standard deviation	± 21.4	± 21.4	
RAND-36 domain Body pain (BP)			
Units: points			
arithmetic mean	51.6	51.6	
standard deviation	± 25.5	± 25.5	
RAND-36 domain Vitality (VT)			
Units: points			
arithmetic mean	16.9	16.9	
standard deviation	± 16.0	± 16.0	

EQ-5D (VAS) Units: points arithmetic mean standard deviation	 38.9 ± 15.9	 38.9 ± 15.9	
EQ-5D-5L (index) Units: points arithmetic mean standard deviation	 0.5 ± 0.2	 0.5 ± 0.2	
Reactive hyperemia index (RHI) Units: points arithmetic mean standard deviation	 2.0 ± 0.6	 2.0 ± 0.6	
Cardiac Index (Nexfin) Units: L/min/m2 arithmetic mean standard deviation	 3.17 ± 0.80	 3.17 ± 0.80	
Chair standing test (CST 30s) Units: No/30s arithmetic mean standard deviation	 12.0 ± 4.2	 12.0 ± 4.2	
6 minute walk test (6MWT) Units: metre arithmetic mean standard deviation	 459.3 ± 135.4	 459.3 ± 135.4	

End points

End points reporting groups

Reporting group title	HBO2
Reporting group description:	
Hyperbaric Oxygen Therapy/Treatment	
Reporting group title	Placebo
Reporting group description:	
Placebo Air, compressed air medical grade	
Subject analysis set title	FAS analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) population includes all randomized subjects who were exposed at least once to the study intervention. FAS subjects were analysed according to their randomised/assigned treatment irrespective of which treatment they actually received.	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety (SAF) population includes all randomized subjects that have received at least one study treatment. SAF patients were analysed according to their actual treatment received.	

Primary: Mean change from baseline to 13 weeks in RAND 36 domains role limitations due to physical function (PF)

End point title	Mean change from baseline to 13 weeks in RAND 36 domains role limitations due to physical function (PF)
End point description:	
End point type	Primary
End point timeframe:	
13 weeks after randomization	

End point values	HBO2	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: RAND-36 score				
arithmetic mean (standard deviation)	9 (± 18.68)	8.59 (± 16.02)		

Statistical analyses

Statistical analysis title	Primary endpoint (PF)
Comparison groups	HBO2 v Placebo

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.04
upper limit	8.29

Primary: Mean change from baseline to 13 weeks in RAND 36 domains role limitations due to physical health (RP).

End point title	Mean change from baseline to 13 weeks in RAND 36 domains role limitations due to physical health (RP).

End point description:

End point type	Primary

End point timeframe:

13 weeks after randomization

End point values	HBO2	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: RAND-36 score				
arithmetic mean (standard deviation)	6.25 (± 20.22)	3.85 (± 16.76)		

Statistical analyses

Statistical analysis title	Primary endpoint (RP)
Comparison groups	HBO2 v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	2.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	10.66

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from inclusion until visit 3. Only serious adverse events (SAEs) were collected outside the treatment period (visit 2). Ongoing AEs and SAEs at the end of visit 3 were followed up until end of trial for each subject.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	HBO2

Reporting group description:

Hyperbaric Oxygen Therapy/Treatment

Reporting group title	Placebo

Reporting group description:

Placebo Air, compressed air medical grade

Serious adverse events	HBO2	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Traumatic haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	HBO2	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 39 (48.72%)	18 / 41 (43.90%)	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	3	
Dizziness			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Epilepsy with myoclonic-atonic seizures			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 39 (5.13%)	5 / 41 (12.20%)	
occurrences (all)	2	5	
Peripheral swelling			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	
occurrences (all)	2	0	

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	5 / 39 (12.82%)	2 / 41 (4.88%)	
occurrences (all)	5	2	
Vertigo			
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Ear discomfort			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Hypoacusis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Subconjunctival haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Dyspnoea			
subjects affected / exposed	4 / 39 (10.26%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	13 / 39 (33.33%)	6 / 41 (14.63%)	
occurrences (all)	13	6	
Skin and subcutaneous tissue disorders			
Livedo reticularis			

subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Paresthesia	Additional description: Paresthesia		
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Neck pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
COVID-19			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2021	Ver 2, 2021-06-30 Protocol updated based on comments from MPA
30 August 2021	Ver 3, 2021-08-30 Substantial amendment submitted to Ethical Review board

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported