



Clinical trial results:

A Randomized, Controlled, Open Label, Multicentre Clinical Trial to explore Safety and Efficacy of Hyperbaric Oxygen for preventing ICU admission, Morbidity and Mortality in Adult Patients With COVID-19 Summary

EudraCT number	2020-001349-37
Trial protocol	SE DE
Global end of trial date	07 February 2022

Results information

Result version number	v1 (current)
This version publication date	12 October 2024
First version publication date	12 October 2024

Trial information

Trial identification

Sponsor protocol code	COVID-19-HBO
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04327505
WHO universal trial number (UTN)	-
Other trial identifiers	Karolinska Institutet: K-1199/2020, Karolinska University Hospital: K-2020/2611

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	Nobels väg 6, Solna, Sweden, 17177
Public contact	Anders Kjellberg, Karolinska Institutet, +46 760657355, anders.kjellberg@ki.se
Scientific contact	Anders Kjellberg, Karolinska Institutet, +46 760657355, anders.kjellberg@ki.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	28 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2022
Global end of trial reached?	Yes
Global end of trial date	07 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate if HBO reduce the number of ICU admissions compared to Best practice for COVID-19

Protection of trial subjects:

The trial was approved by the Swedish Ethical Review Authority (2020-01705) and the Swedish Medical Products Agency (5.1-2020-36673) and conducted in accordance with the declaration of Helsinki and ICH-GCP. Participants provided written informed consent before enrollment.

The trial was monitored by KTA, an independent organisation before the trial started, during the trial conduct and after the trial was completed, to ensure that the trial was carried out according to the protocol and that data were collected, documented and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring was performed as per the trial's monitoring plan and to ensure that the subject's rights, safety and well-being were met as well as data in the eCRF are complete, correct and consistent with the source data. The monitoring was performed by an independent experienced monitor qualified in ICH-GCP, applicable national and international regulations and the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2020
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: 31
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	16
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between June 4, 2020, and Dec 1, 2021, 79 patients were assessed for eligibility, 34 subjects were randomly assigned to Hyperbaric Oxygen Therapy (HBOT, N=18) or best practise (BP, N=16). The trial was prematurely terminated for futility.

Pre-assignment

Screening details:

Patients 18–90 years, hospitalised for severe COVID–19 with moderate to severe ARDS, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂) below 200 mmHg (26.7 kPa), based on arterial blood gas measurement with at least 2 risk factors for increased risk of ICU admission/mortality, likely to need intubation.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open label trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Hyperbaric oxygen

Arm description:

The HBOT group received in addition to best practice: HBOT with medical oxygen 100%, 2.4 ATA for 80–90 min, with two five-min air-breaks, once a day, maximum five treatments within seven days from randomisation in addition to best practice.

Arm type	Experimental
Investigational medicinal product name	Conoxia 100%, Medicinal gas, cryogenic
Investigational medicinal product code	SUB14733MIG
Other name	
Pharmaceutical forms	Medicinal gas, cryogenic
Routes of administration	Inhalation use

Dosage and administration details:

The HBOT group received in addition to best practice: HBOT with medical oxygen 100%, 2.4 ATA for 80–90 min, with two five-min air-breaks, once a day, maximum five treatments within seven days from randomisation in addition to best practice.

Arm title	Best practice
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Arm description:

Received best practice treatment for COVID–19, including normobaric medical oxygen 100% administered as needed, low dose steroids, low molecular weight heparin.

Arm type	Best practice
Investigational medicinal product name	Conoxia 100%, Medicinal gas, compressed
Investigational medicinal product code	SUB14733MIG
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

Received best practice treatment for COVID–19, including normobaric medical oxygen 100% administered as needed.

Number of subjects in period 1	Hyperbaric oxygen	Best practice
Started	18	16
Completed	12	15
Not completed	6	1
Adverse event, serious fatal	4	-
Consent withdrawn by subject	2	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall period
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Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	34	34	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	65.4		
standard deviation	± 9.5	-	
Gender categorical			
Units: Subjects			
Female	15	15	
Male	19	19	
Concomitant medications: Dexamethasone/Betamethasone			
Units: Subjects			
Yes	32	32	
No	2	2	
Concomitant medication: LMWH			
Units: Subjects			
Yes	33	33	
No	1	1	
Concomitant medication: Remdesivir			
Units: Subjects			
Yes	11	11	
No	23	23	
Concomitant medication: Rituximab			
Units: Subjects			
Yes	1	1	
No	33	33	
Concomitant medication: Tocilizumab			
Units: Subjects			
Yes	3	3	
No	31	31	
Concomitant medication: Casirivimab/Imdevimab			
Units: Subjects			
Yes	1	1	
No	33	33	
Concomitant medication: Methotrexate			
Units: Subjects			
Yes	1	1	
No	33	33	

End points

End points reporting groups

Reporting group title	Hyperbaric oxygen
Reporting group description: The HBOT group received in addition to best practice: HBOT with medical oxygen 100%, 2·4 ATA for 80–90 min, with two five–min air–breaks, once a day, maximum five treatments within seven days from randomisation in addition to best practice.	
Reporting group title	Best practice
Reporting group description: Recieved best practice treatment for COVID–19, including normobaric medical oxygen 100% administrated as needed, low dose steroids, low molecular weight heparin.	

Primary: ICU Admission

End point title	ICU Admission
End point description:	
End point type	Primary
End point timeframe: Until EOT, 30 days.	

End point values	Hyperbaric oxygen	Best practice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: Percent				
ICU Admission: Yes	13	5		
ICU Admission: No	5	10		

Statistical analyses

Statistical analysis title	Proportion of subjects selected for ICU
Comparison groups	Hyperbaric oxygen v Best practice
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	10.39

Notes:

[1] - Primary endpoint evaluated at the type I error rate of 0.05 using a two-sided test. There was no adjustment for multiplicity as there were only one primary endpoint and secondary endpoints are to be interpreted as exploratory. Corrected for gender.

Secondary: Mortality

End point title	Mortality
End point description: 30-day mortality, all-cause	
End point type	Secondary
End point timeframe: Until EOT, 30 days	

End point values	Hyperbaric oxygen	Best practice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: Subjects deceased	4	1		

Statistical analyses

Statistical analysis title	Mortality, time to event
Comparison groups	Hyperbaric oxygen v Best practice
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Logrank

Secondary: Time-to-Intubation

End point title	Time-to-Intubation
End point description:	
End point type	Secondary
End point timeframe: Until EOT, 30 days	

End point values	Hyperbaric oxygen	Best practice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: Days				
arithmetic mean (confidence interval 95%)	25.3 (19.7 to 30.9)	24.5 (19.8 to 29.3)		

Statistical analyses

Statistical analysis title	Time-to-Intubation difference
Comparison groups	Hyperbaric oxygen v Best practice
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	Logrank

Secondary: Time-to-ICU

End point title	Time-to-ICU
End point description:	
End point type	Secondary
End point timeframe:	
Until EOT, 30 days	

End point values	Hyperbaric oxygen	Best practice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: Cumulative ICU free days				
number (not applicable)	1	14		

Statistical analyses

Statistical analysis title	Difference in cumulative ICU free days
Comparison groups	Hyperbaric oxygen v Best practice

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 ^[2]
Method	Logrank

Notes:

[2] - Median time 14.0 for Best Practice vs 1.0 for HBOT.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Until EOT, 30 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	All study subjects
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Reporting group description: -

Serious adverse events	All study subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 34 (47.06%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	5		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Endotracheal intubation			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Death			
subjects affected / exposed	5 / 34 (14.71%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	8 / 34 (23.53%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 2		
Pneumothorax			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All study subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 34 (82.35%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		

Thrombophlebitis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 4		
Bradycardia subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2		
Chest pain subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Ventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3		
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
General disorders and administration site conditions Fever subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Shivering subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 7		
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	12 / 34 (35.29%)		
occurrences (all)	15		
Pneumomediastinum			
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Claustrophobia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		

Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		
Infections and infestations Abscess subjects affected / exposed occurrences (all) Bacteraemia subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Fungal infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 34 (2.94%) 1 2 / 34 (5.88%) 2 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Malnutrition subjects affected / exposed occurrences (all)	 2 / 34 (5.88%) 2 1 / 34 (2.94%) 1 2 / 34 (5.88%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2020	V3, Change of sites
27 February 2021	V4, Change of limits for safety endpoints and reporting (Safety was re-assessed after Safety interim analysis)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/39059726>