



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 |
|-----------------------|--------------|

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 |
|------------------|---------------|

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 |
|--------------------------------|----------------|
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | All study subjects |
|-----------------------|--------------------|

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>