



Clinical trial results: Inhaled Nitric Oxide Gas Therapy in Mechanically Ventilated Patients with Severe Acute Respiratory Syndrome in COVID-19

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-001490-68 |
| Trial protocol | SE |
| Global end of trial date | 15 April 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 July 2022 |
| First version publication date | 30 July 2022 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NCT04306393 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04306393 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Danderyd Hospital |
| Sponsor organisation address | Entrévagen 2, Danderyd, Sweden, 18257 |
| Public contact | Dept of Medicine and Infection, Danderyd Hospital, +46 8123 550 00, magnus.hedenstierna@regionstockholm.se |
| Scientific contact | Dept of Medicine and Infection, Danderyd Hospital, +46 8123 550 00, magnus.hedenstierna@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 | 13 July 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 April 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to measure the difference in ventilator treatment time between the iNO and the control group.

Protection of trial subjects:

All patients were in ICU on mechanical ventilation sedated and provided analgesia for mechanical controlled ventilation

Background therapy:

Full ICU therapy

Evidence for comparator:

Pure oxygen to add to the inspired gas mixture

| | |
|---|-------------|
| Actual start date of recruitment | 03 May 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Sweden: 40 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 40 |

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) | 23 |
| From 65 to 84 years | 17 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients with confirmed COVID-19 infection admitted to Danderyd hospital and in need of mechanical ventilation were included in the study. Recruitment started in may 2020 and ended in january 2021.

Pre-assignment

Screening details:

All participants were required to sign informed consent and therefore screening was performed before intubation/mechanical ventilation. In total 100 subjects were screened for inclusion. Of these 43 never needed mechanical ventilation and were not randomized. Another 17 did not sign informed consent.

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Active INO |

Arm description:

Inhaled nitric oxide 80 ppm in decreasing dose

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | INOmax |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Medicinal gas, compressed |
| Routes of administration | Respiratory use |

Dosage and administration details:

80 ppm at start and reduced to 40 ppm until hypoxia resolved

| | |
|------------------|---------|
| Arm title | Control |
|------------------|---------|

Arm description:

Control O2

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Active INO | Control |
|--------------------------------|------------|---------|
| Started | 21 | 19 |
| Completed | 21 | 19 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | over all trial |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values | over all trial | Total | |
|---|----------------|-------|--|
| Number of subjects | 40 | 40 | |
| 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 | | | |
| median | 61 | | |
| full range (min-max) | 26 to 79 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 8 | |
| Male | 32 | 32 | |

End points

End points reporting groups

| | |
|--|------------|
| Reporting group title | Active INO |
| Reporting group description: Inhaled nitric oxide 80 ppm in decreasing dose | |
| Reporting group title | Control |
| Reporting group description: Control O2 | |

Primary: duration of mechanical ventilation

| | |
|--|------------------------------------|
| End point title | duration of mechanical ventilation |
| End point description: Days on mechanical ventilation | |
| End point type | Primary |
| End point timeframe: During study period | |

| End point values | Active INO | Control | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 19 | | |
| Units: days | 11 | 8 | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Time to extubation (F-G Competing risks)/F&G extubation.tif |
|-----------------------------------|---|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Duration of mechanical ventilation (days) |
| Comparison groups | Active INO v Control |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.471 |
| Method | Fine and Gray competing risks model |

Secondary: All cause mortality at 28 days

| | |
|------------------------|--------------------------------|
| End point title | All cause mortality at 28 days |
| End point description: | |
| End point type | Secondary |

End point timeframe:

All cause mortality 28 days after randomization

| End point values | Active INO | Control | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 19 | | |
| Units: Proportion alive | | | | |
| Alive | 12 | 11 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | All cause mortality at 28 days/28 d mortalitet.tif |
|-----------------------------------|--|

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | All cause mortality at 28 days |
| Comparison groups | Active INO v Control |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.96 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 2.76 |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

During study period

Adverse event reporting additional description:

AEs according to regulations

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|----------|
| Dictionary name | Clinical |
|-----------------|----------|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | Active |
|-----------------------|--------|

Reporting group description:

INO

| | |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: All patients were ICU treated with mechanical ventilation, sedated, thus it was not possible to separate from the clinical course

| Serious adverse events | Active | Control | |
|---|--|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 21 (47.62%) | 10 / 19 (52.63%) | |
| number of deaths (all causes) | 9 | 8 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Death | | | |
| subjects affected / exposed | 9 / 21 (42.86%) | 8 / 19 (42.11%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 9 | 0 / 8 | |
| ECMO | Additional description: Severe ARDS and need for transfer to ECMO unit | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 19 (10.53%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Active | Control | |
|---|----------------|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 19 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported