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 requiered 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	
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