Clinical trial results:
Efficacy and safety of 72-hour infusion of Prostacyclin (1 ng/kg/min) in patients with COVID-19 induced respiratory failure – a multicentre randomized, placebo-controlled, blinded, investigator-initiated trial

Summary

EudraCT number	2020-001296-33
Trial protocol	DK
Global end of trial date	26 April 2021

Results information

Result version number	v1 (current)
This version publication date	15 June 2022
First version publication date	15 June 2022

Trial information

Trial identification

Sponsor protocol code	COMBAT-COVID-19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04420741
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Pär Johansson, Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen University Hospital, +45 35452030, per.johansson@regionh.dk
Scientific contact	Pär Johansson, Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen University Hospital, 35452030 35452030, per.johansson@regionh.dk

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 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2021
Global end of trial reached?	Yes
Global end of trial date	26 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate whether continuous infusion of iloprost at a dose of 1 ng/kg/min for 72-hours reduces the severity of respiratory failure in the ICU as compared to placebo.

Protection of trial subjects:

Patients included in this trial is admitted to the ICU with COVÌD19 requiring respiratory support, therefore these patients will receive the best possible care and monitored closely during their hospital stay.

Background therapy:

Standard of care for treatment of COVID19

Evidence for comparator:

Crystalloids are the recommended volume therapy for patients with septic. We have therefore chosen that the placebo should be saline 0.9 % (NaCl) to maintain blinding in the trial as iloprost is diluted in saline. Patients receiving placebo will receive an equal volume of fluid administered in the same way as the iloprost infusion.

Actual start date of recruitment	01 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	Denmark: 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)	34

From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients are recruited in the periode fra June 2020 to January 2021 in one of the 5 ICU2 in the Capital Region of Denmark.

Pre-assignment

Screening details:

Patients are subject for screening if they are 18 years old or above and admitted to an ICU with confirmed COVID19 infection requirering mechanical ventilation.
However patients can only be included if souble thrombomodulin is 4 ng/mL or above.

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	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The trial is double-blinded with saline 0.9 % (NaCl) as placebo to maintain blinding. iloprost is diluted in saline and therefore both solutions are colorless fluids. Patients receiving placebo will receive an equal volume of fluid administered in the same way as the iloprost infusion. The preparation of trial medication will be done by an unblinded nurse, outside the ICU´s, who will be responsible for preparing the investigational drug so that it can be administered in blinded fashion.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention arm

Arm description:

Iloprost (Ilomedin®) is a marketed product which will be administered in this trial as the IMP.

Arm type	Experimental
Investigational medicinal product name	Ilomedin
Investigational medicinal product code	
Other name	Prostacyclin
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

All patients will receive 72-hour continuous infusion of either active investigational drug or placebo. Patients on active treatment will receive continuous infusion of 1.0 ng/kg/min iloprost. The infusion volume of the active investigational drug and placebo will be 72 ml per 24h.

Arm title	Placebo arm

Arm description:

Saline 0.9% is used as comparator

Arm type	Placebo
Investigational medicinal product name	Saline 0.9%
Investigational medicinal product code	
Other name	sodium chloride
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

All patients will receive 72-hour continuous infusion of either active investigational drug or placebo. Patients on placebo will receive continuous infusion equivalent to iloprost. The infusion volume of the active investigational drug and placebo will be 72 ml per 24h.

Number of subjects in period 1	Intervention arm	Placebo arm
Started	41	39
Completed	41	39

Baseline characteristics

Reporting groups	
Reporting group title	Intervention arm
Reporting group description:	
Iloprost (Ilomedin®) is a marketed product which will be administered in this trial as the IMP.	
Reporting group title	Placebo arm
Reporting group description:	
Saline 0.9% is used as comparator	

Reporting group values	Intervention arm	Placebo arm	Total
Number of subjects	41	39	80
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	18	34
From 65-84 years	25	21	46
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	11	16	27
Male	30	23	53

End points

End points reporting groups	
Reporting group title	Intervention arm
Reporting group description: Iloprost (Ilomedin®) is a marketed product which will be administered in this trial as the IMP.	
Reporting group title	Placebo arm
Reporting group description: Saline 0.9% is used as comparator	

Primary: Days alive without mechanical care	
End point title	Days alive without mechanical care
End point description: Number of days alive and without mechanical ventilation in the ICU for the intention to treat population	
End point type	Primary
End point timeframe: Number of days from baseline to dag 28	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Days				
median (standard deviation)				
Number of free days	16 (± 12)	5 (± 10)		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description: for the ITT population	
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Mortality day 28	
End point title	Mortality day 28

End point description: Number of deaths from baseline to day 28	
End point type	Secondary
End point timeframe: At day 28	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Number				
Number of deaths	9	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality day 90

End point title	Mortality day 90
End point description: Number of deaths from baseline to day 90	
End point type	Secondary
End point timeframe: Day 90	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Number				
Number of deaths	13	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive without vasopressor day 28

End point title	Days alive without vasopressor day 28
End point description: Number of days alive and without vasopressor in the ICU	
End point type	Secondary

End point timeframe:

Number of days from baseline to dag 28

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Days				
Number of free days	22	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive without vasopressor day 90

End point title	Days alive without vasopressor day 90

End point description:

Number of days alive and without vasopressor in the ICU

End point type	Secondary

End point timeframe:

Number of days from baseline to dag 90

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Days				
Number of free days	84	59		

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive without renal replacement therapy day 28

End point title	Days alive without renal replacement therapy day 28

End point description:

Number of days alive and without RRT in the ICU

End point type	Secondary

End point timeframe:

Number of days from baseline to dag 28

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Days				
Number of free days	28	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive without renal replacement therapy day 90

End point title	Days alive without renal replacement therapy day 90

End point description:

Number of days alive and without RRT in the ICU

End point type	Secondary

End point timeframe:

Number of days from baseline to dag 90

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Days				
Number of free days	90	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious adverse events

End point title	Serious adverse events

End point description:

End point type	Secondary

End point timeframe:

Number of events from baseline to dag 7

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Number				
SAE	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious adverse reaction

End point title	Serious adverse reaction

End point description:

End point type	Secondary

End point timeframe:

Number of reactions from baseline to dag 7

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Events				
Reactions	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive without mechanical care day 90

End point title	Days alive without mechanical care day 90

End point description:

Number of days alive and without mechanical ventilation in the ICU

End point type	Secondary

End point timeframe:

Number of days from baseline to dag 90

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Days				
Number of free days	77	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

SAE and SAR are collected from baseline to day 7

Adverse event reporting additional description:

Only selected serious adverse events and serious adverse reaction are collected as these patients are severily ill. Therefore, recording of all AE and SAEs in the CRF will not add valuable information to the patient's safety in this trial and will make it difficult be distinguish the real safety signal and those sight of the significant reactions

Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	0

Reporting groups

Reporting group title	Overall trail

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: Only certain SAE is reported in this trial due to the severity ilness of the incluted patients

Serious adverse events	Overall trail		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 80 (7.50%)		
number of deaths (all causes)	32		
number of deaths resulting from adverse events	0		
Vascular disorders			
Bleeding	Additional description: Bleeding events requiring more than 2 RBCs within 24 hours or ongoing bleeding		
subjects affected / exposed	2 / 80 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
limb ischaemia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal ischaemia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			

subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Overall trail		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 80 (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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34813414