



## Clinical trial results:

**“Efficacy and safety of 72-hour infusion of Prostacyclin (1 ng/kg/min) in patients with septic shock induced endotheliopathy – a multicentre randomized, placebo-controlled, blinded, investigator-initiated trial”**

### Summary

EudraCT number	2019-001131-31
Trial protocol	DK
Global end of trial date	28 June 2022

### Results information

Result version number	v1 (current)
This version publication date	23 November 2024
First version publication date	23 November 2024

### Trial information

#### Trial identification

Sponsor protocol code	COMBAT-SHINE
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04123444
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Jakob Stensballe, Section for transfusion Medicines, Capital Region Blood Bank, Copenhagen University Hospital, +45 354538587, jakob.stensballe@regionh.dk
Scientific contact	Jakob Stensballe, Section for transfusion Medicines, Capital Region Blood Bank, Copenhagen University Hospital, +45 35458587, jakob.stensballe@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	07 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2022
Global end of trial reached?	Yes
Global end of trial date	28 June 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective in this trial is to investigate whether continuous infusion of iloprost at a dose of 1 ng/kg/min for 72-hours is safe and significantly reduce organ failure score in the ICU compared to infusion of placebo in patients with septic shock and SHINE.

Protection of trial subjects:

Patients included in this trial is admitted to the ICU with septic shock, therefore these patients will receive the best possible care and monitored closely during their hospital stay. All included patients and/or next-of-kin will sign informed consent to participate.

Background therapy:

Standard of care for treatment for septic shock

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	30 October 2019
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	Denmark: 279
Worldwide total number of subjects	279
EEA total number of subjects	279

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)	107
From 65 to 84 years	163
85 years and over	9

## Subject disposition

### Recruitment

Recruitment details:

Patients are recruited in the periode from October 30, 2019 to April 6, 2022 in one of the 5 ICUs in the Capital Region of Denmark and at the ICU in Region Zealand University Hospital.

### Pre-assignment

Screening details:

Patients are subject for screening if they are 18 years old or above and admitted the ICU with confirmed septic shock. Septic shock, defined as (i) suspected or documented infection, (ii) persisting hypotension requiring vasopressors to maintain MAP  $\geq 65$  mm Hg AND (iii) lactate level  $>2$  mmol/L despite fluid therapy.

### 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, Carer, 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 facion.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	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 ng/kg/min iloprost. The infusion volume of the active investigational drug and placebo will be 72 ml per 24h.

<b>Arm title</b>	Placebo arm
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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 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.

<b>Number of subjects in period 1</b>	Intervention arm	Placebo arm
Started	142	137
Completed	142	137

## 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	142	137	279
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)	49	58	107
From 65-84 years	86	77	163
85 years and over	7	2	9
Gender categorical Units: Subjects			
Female	54	53	107
Male	88	84	172

## 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: Mean daily modified Sequential Organ Failure Assessment (SOFA) score

End point title	Mean daily modified Sequential Organ Failure Assessment (SOFA) score
End point description: Mean daily SOFA score during ICU admission up to day 90 for the intention to treat population	
End point type	Primary
End point timeframe: From Baseline up to day 90	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	136		
Units: number				
number (confidence interval 95%)	10.6 (6.4 to 14.8)	10.5 (5.9 to 15.5)		

### Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description: For the ITT analysis	
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7
Method	ANCOVA
Parameter estimate	IQR
Confidence interval	
level	95 %
sides	2-sided

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**Secondary: Mortality day 28**

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End point title	Mortality day 28
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End point description:

Number of death from baseline until day 28

End point type	Secondary
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End point timeframe:

From baseline until day 90

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End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	136		
Units: Days	70	60		

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**Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information<sup>[1]</sup>

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 severely 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 to distinguish the real safety signal and those signs of the significant reactions.

Assessment type	Systematic
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### Dictionary used

Dictionary name	none
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Dictionary version	0
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### Reporting groups

Reporting group title	Overall
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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 illness of the included patients

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 279 (16.49%)		
number of deaths (all causes)	151		
number of deaths resulting from adverse events	0		
Investigations			
Investigation			
subjects affected / exposed	3 / 279 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Ischemia	Additional description: Includes cerebral ischemia, myocardial ischemia, limb ischemia and intestinal ischemia		
subjects affected / exposed	30 / 279 (10.75%)		
occurrences causally related to treatment / all	1 / 30		
deaths causally related to treatment / all	0 / 0		
Bleeding risk assessment	Additional description: Bleeding events, meaning cerebral hemorrhage, gastrointestinal bleeding and other bleedings		
subjects affected / exposed	19 / 279 (6.81%)		
occurrences causally related to treatment / all	0 / 19		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			

subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 279 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure	Additional description: severe heart failure		
subjects affected / exposed	5 / 279 (1.79%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 279 (0.00%)		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2019	Description of change: Modification of doses volume as not enough volume to prime the infusion set.
12 November 2020	Description of changes: Addition blood sample for sub study of 20 patients and a corresponding healthy cohort

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported