



Clinical trial results:

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

Summary

EudraCT number	2019-000936-24
Trial protocol	DK NO
Global end of trial date	12 November 2021

Results information

Result version number	v1 (current)
This version publication date	24 January 2024
First version publication date	24 January 2024

Trial information

Trial identification

Sponsor protocol code	SHINE-TRAUMA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03903939
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Pär I Johansson, Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen University Hospital, +45 35452030, per.johansson@regionh.dk
Scientific contact	Pär I 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	20 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2021
Global end of trial reached?	Yes
Global end of trial date	12 November 2021
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 increase the number of ICU free days, within 28 days from admission compared to infusion of placebo in trauma patients with haemorrhagic shock and SHINE.

Protection of trial subjects:

Patients included in this trial is admitted to the trauma center, therefore these patients will receive the best possible care and monitored closely during their hospital stay.

Background therapy:

Standard of care

Evidence for comparator:

These patients receive a lot of fluid and blood product upon arrival at the trauma center. Saline 0.9 % (NaCl) is chosen as comparator 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	03 June 2019
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	Norway: 47
Country: Number of subjects enrolled	Denmark: 182
Worldwide total number of subjects	229
EEA total number of subjects	229

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)	171
From 65 to 84 years	50
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Patients were recruited upon admission to the trauma center with the need for activation of massive transfusion protocol due to trauma.

Only patient at 18 years of age or above were included.

Pre-assignment

Screening details:

Patients are subject for screening if they are admitted to the trauma center with hemorrhagic shock requiring massive blood transfusion.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, 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 study staff, 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	Solution for 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
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Arm description:

Saline 0.9% is used as comparator. Given in equal volumen as investigational drug

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	119	110
Completed	116	105
Not completed	3	5
Consent withdrawn by subject	1	3
Adverse event, non-fatal	2	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall
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Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	229	229	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	171	171	
From 65-84 years	50	50	
85 years and over	8	8	
Gender categorical			
Units: Subjects			
Female	47	47	
Male	182	182	

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. Given in equal volumen as investigational drug	

Primary: ICU free days

End point title	ICU free days
End point description: Mean number of days alive and not admitted to an intensive care unit	
End point type	Primary
End point timeframe: Baseline to day 28	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: day				
number (not applicable)	15.65	13.99		

Statistical analyses

Statistical analysis title	Primary endpoint - ITT
Statistical analysis description: Mean days	
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2844
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6338
upper limit	1.378

Primary: ICU free days - PP

End point title	ICU free days - PP
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End point description:

Number of days alive and not admitted to an intensive care unit - measured for the Per Protocol analysis

End point type	Primary
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End point timeframe:

Baseline to day 28

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	105		
Units: day				
number (not applicable)	15.83	13.98		

Statistical analyses

Statistical analysis title	Primary endpoint - Per protocol
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Comparison groups	Intervention arm v Placebo arm
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Number of subjects included in analysis	221
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Analysis specification	Pre-specified
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Analysis type	other
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P-value	= 0.2269
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Method	Regression, Linear
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Parameter estimate	Mean difference (net)
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Point estimate	-1.861
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-4.886
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upper limit	1.165
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Secondary: Mortality day 28

End point title	Mortality day 28
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End point description:

Percentage dead from baseline to day 28

End point type	Secondary
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End point timeframe:

Baseline to day 28

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: percent				
number (not applicable)	18.8	19.63		

Statistical analyses

Statistical analysis title	Secondary endpoint (ITT) - Mortality day28
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5751
upper limit	1.755
Variability estimate	Standard deviation

Secondary: Mortality day 90

End point title	Mortality day 90
End point description:	
Percentage dead from baseline to day 90	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: percent				
number (not applicable)	19.83	20.19		

Statistical analyses

Statistical analysis title	Secondary endpoint (ITT) - Mortality day90
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.9863
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5582
upper limit	1.704
Variability estimate	Standard deviation

Secondary: Lenght of stay

End point title	Lenght of stay
End point description:	
Mean number of days admitted to the hospital until day 90	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: day				
number (not applicable)	19.96	27.32		

Statistical analyses

Statistical analysis title	Secondary endpoint (ITT) - Length of stay
Comparison groups	Placebo arm v Intervention arm

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01285
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	7.838
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.66
upper limit	14.02

Secondary: Vasopressor free days

End point title	Vasopressor free days
End point description:	
Number of days alive and without use of vasopressor until day 28	
End point type	Secondary
End point timeframe:	
Baseline to day 28	

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: day				
number (not applicable)	19.86	18.07		

Statistical analyses

Statistical analysis title	Secondary endpoint (ITT) - Vasopressor free days
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2118
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.442
upper limit	0.9426

Secondary: Ventilator free days

End point title	Ventilator free days
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End point description:

Number of days alive and without use of mechanical ventilation until day 28

End point type	Secondary
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End point timeframe:

Baseline to day 28

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: day				
number (not applicable)	18.03	16.4		

Statistical analyses

Statistical analysis title	Secondary endpoint (ITT) - Ventilator free days
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3064
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-1.576
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.625
upper limit	1.474

Secondary: RRT free days

End point title	RRT free days
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End point description:

Number of days alive and without use of renal replacement therapy (RRT) until day 28

End point type	Secondary
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End point timeframe:

baseline to day 28

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: day				
number (not applicable)	23.11	22.99		

Statistical analyses

Statistical analysis title	Secondary endpoint (ITT) - RRT free days
Comparison groups	Intervention arm v Placebo arm
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9841
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.02558
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	2.541

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Baseline to day 4

Adverse event reporting additional description:

Only SAEs and SARs were recorded due to the severity of the condition treated

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: There are no non-serious adverse events recorded for these results. 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	9 / 9 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intracerebral haematoma evacuation			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	4 / 9 (44.44%)		
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	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 9 (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/37962189>