Clinical trial results:

Safety and efficacy of iloprost and eptifibatide co-administration compared to standard therapy in patients with septic shock – a randomized, controlled, double-blind investigator-initiated trial (CO-ILEPSS)

Summary

EudraCT number	2014-002440-41
Trial protocol	DK
Global end of trial date	01 April 2017

Results information

Result version number	v1 (current)
This version publication date	30 April 2020
First version publication date	30 April 2020
Summary attachment (see zip file)	Results summary (Results_letter from sponsor.pdf)

Trial information

Trial identification

Sponsor protocol code	CO-ILEPSS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02204852
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet, Capital Region Bloodbank 2034
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Sponsor (Sisse Ostrowski), Rigshospitalet, Capital Region Bloodbank 2034, Section for Transfusion Medicine, 0045 24430464, sisse.ostrowski@gmail.com
Scientific contact	Sponsor (Sisse Ostrowski), Rigshospitalet, Capital Region Bloodbank 2034, Section for Transfusion Medicine, 0045 24430464, sisse.ostrowski@gmail.com

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	23 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2017
Global end of trial reached?	Yes
Global end of trial date	01 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluating the safety and efficacy of iloprost and eptifibatide co-administration compared to placebo as an addition to standard care in septic shock patients.

Protection of trial subjects:

The inclusion and exclusion criteria specific ensure that the patients included in this trial have a medical condition that ensure the safety for the patients e.g.
platelet count more than 10,000/mm3 in the previous 24 hours; no need of blood products for bleeding in the previous 24 hours and no treatment with any antithrombotics within 12 hours.
The dose used of iloprost and eptifibatide are lower than the recommended doses for their respective approved indications. The used doses are considered safety. However, stopping rules are listed in the protocol and if any of the following are seen the trial treatment will be stopped e.g. allergic reactions, severe bleeding, severe hypotension, severe hypoxia or clinically relevant thrombosis.
All patients are admitted to the ICU during study treatment and will be treated according to local requirement is any SAE/SAR are seen.

Background therapy:

All patients will receive standard of care for treatment of septic shock.

Evidence for comparator:

The intervention is tested against standard of care. No comparator is used.

Actual start date of recruitment	01 September 2014
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: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	12
From 65 to 84 years	11
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The patients are recruited at the ICU at North Zealand Hospital, Denmark for a period of 20 months.
Only adult patient admitted to the ICU, fulfilling the criteria for septic shock can be included.
Patients are presented at the investigator site in a critical acute condition therefore a scientific guardian
will co-sign the informed consent form.

Pre-assignment

Screening details:

All patients admitted to the ICU present with signs of septic shock are screened for inclusion. If any of
the exclusion criteria are fulfilled the patient can enter the trial. A total of 509 are assessed for eligibility
-n=281 not meeting inclusion criteria, n=158 due to exclusion criteria, n=29 included in another studie,
n=17 missed inclusion.

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	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Blinding implementation details:

The trial was a double-blind trial. Sealed envelopes are used for randomisation. Both trial medication
were colourless when diluted in the saline and it was impossible to distinguish from each other. Trial
medication will be handled by unblinded study nurse.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iloprost/eptifibatide

Arm description:

co-administration of iloprost and eptifibatide in addition to standard of care

Arm type	Experimental
Investigational medicinal product name	EPTIFIBATIDE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

continuous co-administration of i.v infusions of 0.50 µg/kg/min eptifibatide for 48 hours.

Investigational medicinal product name	ILOPROST TROMETAMO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

continuous co-administration of i.v infusions of 1.0 ng/kg/min of iloprost for 48 hours

Arm title	Placebo

Arm description:

Placebo in addition to standard of care

Arm type	Placebo

Investigational medicinal product name	Saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients in the placebo group will receive double dummy saline infusions and will be treated exactly as active patients.

Number of subjects in period 1	Iloprost/eptifibatide	Placebo
Started	15	9
Completed	12	6
Not completed	3	3
Physician decision	1	-
incorret inclusion	-	1
Adverse event, non-fatal	1	1
transfer to other hospital	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	24	24	
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	12	
From 65-84 years	11	11	
85 years and over	1	1	
Gender categorical			
Overall trial			
Units: Subjects			
Female	7	7	
Male	17	17	

Subject analysis sets

Subject analysis set title	PP - Intervention group
Subject analysis set type	Per protocol

Subject analysis set description:

Patients in the intervention group who completed the 7-day trial period

Subject analysis set title	PP - Placebo group
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who completed the 7-day trial period

Reporting group values	PP - Intervention group	PP - Placebo group	
Number of subjects	12	6	
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	3	
From 65-84 years	5	3	
85 years and over	0	0	
Gender categorical			
Overall trial			
Units: Subjects			
Female	4	0	
Male	8	6	

End points

End points reporting groups

Reporting group title	Iloprost/eptifibatide
Reporting group description:	
co-administration of iloprost and eptifibatide in addition to standard of care	
Reporting group title	Placebo
Reporting group description:	
Placebo in addition to standard of care	
Subject analysis set title	PP - Intervention group
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients in the intervention group who completed the 7-day trial period	
Subject analysis set title	PP - Placebo group
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who completed the 7-day trial period	

Primary: Changes in platelet count

End point title	Changes in platelet count
End point description:	
Time depended changes in platelet count from baseline to 48 hours post-randomisation in the per protocol group	
End point type	Primary
End point timeframe:	
48-hours post baseline	

End point values	PP - Intervention group	PP - Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: 10^9/L				
median (inter-quartile range (Q1-Q3))				
Platelet count - Baseline	187.5 (130 to 254.5)	212 (149 to 295.3)		
Platelet count - 48h	126.5 (99 to 297.8)	131 (109.5 to 264.3)		

Statistical analyses

Statistical analysis title	Change in platelet count - placebo
Statistical analysis description:	
Change from baseline to 48 hours	
Comparison groups	PP - Placebo group v PP - Intervention group

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.049
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Exploratory

Statistical analysis title

Statistical analysis title	Change in platelet count - Intervention

Statistical analysis description:

Change from baseline to 48 hours

Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Exploratory

Statistical analysis title	Change in platelet count - Time x group

Statistical analysis description:

Change from baseline to 48 hours between groups

Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.83
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Exploratory

Primary: Change in endothelial biomarkers

End point title	Change in endothelial biomarkers

End point description:

Time-dependent change in absolute endothelial biomarker values from baseline to 48-hours

End point type	Primary

End point timeframe:

At 48-hours post baseline

End point values	PP - Intervention group	PP - Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))				

Thrombomodulin - Baseline	9.1 (6.6 to 17.9)	16.1 (10.9 to 18.8)		
Thrombomodulin - 48h	8 (5.9 to 13)	14.6 (10.6 to 19)		
sE-Selectin - Baseline	175.2 (82.9 to 236)	184.9 (149.7 to 229.8)		
sE-Selectin - 48h	161.2 (82.3 to 210)	153.2 (132.3 to 212.5)		
Syndecan1 - Baseline	56 (44.8 to 98)	111.3 (55.7 to 118.1)		
Syndecan1 - 48h	92.2 (50.9 to 110.3)	111 (58.7 to 120.9)		
sVE-Cadherin - Baseline	1447.2 (1391.8 to 1748.9)	2084.9 (1917.7 to 2520.3)		
sVE-cadherin - 48h	1530.8 (1422.4 to 1751.6)	1934.5 (1871.1 to 2272.8)		

Statistical analyses

Statistical analysis title	Change in Thrombomodulin from baseline to 48h
Statistical analysis description:	
Change in biomarker thrombomodulin from baseline to 48 hours post-randomisation	
Comparison groups	PP - Placebo group v PP - Intervention group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.851 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Exploratory

[5] - Time x group

Statistical analysis title	Change in sE-Selectin from baseline to 48h
Statistical analysis description:	
Change in biomarker sE-Selectine from baseline to 48 hours post-randomisation	
Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.659 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Exploratory

[7] - Time x group

Statistical analysis title	Change in syndecan-1 from baseline to 48h
Statistical analysis description:	
Change in biomarker syndecain-1 from baseline to 48 hours post-randomisation	
Comparison groups	PP - Intervention group v PP - Placebo group

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.566 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Exploratory

[9] - Time x group

Statistical analysis title	Change in sVE-cadherin from baseline to 48h

Statistical analysis description:

Change in biomarker sVE-cadherin from baseline to 48 hours post-randomisation

Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.292 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - Exploratory

[11] - Time x group

Primary: Change in endothel biomarker - nucleosomes

End point title	Change in endothel biomarker - nucleosomes

End point description:

Time-dependent change in endothelial biomarker nucleosome

End point type	Primary

End point timeframe:

At 48-hours post baseline

End point values	PP - Intervention group	PP - Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: Percentage				
median (inter-quartile range (Q1-Q3))				
Nucleosomes - Baseline	13.3 (4.6 to 15.4)	7.3 (4.2 to 23.2)		
Nucleosomes - 48h	10.8 (4.2 to 18.8)	19.5 (11.9 to 24.2)		

Statistical analyses

Statistical analysis title	Changes in nucleosomes (Baseline to 48h)

Statistical analysis description:

Change i biomarker nucleosomes from baseline to 48 hours post-randomisation

Comparison groups	PP - Intervention group v PP - Placebo group

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.421 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - Exploratory

[13] - Time x group

Primary: Change in D-dimer and fibrin split products

End point title	Change in D-dimer and fibrin split products

End point description:

Change in D-dimer and fibrin slit products indicative of fibrinolysis at 48-hours from baseline

End point type	Primary

End point timeframe:

At 48-hours post baseline

End point values	PP - Intervention group	PP - Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))				
D-dimer -Baseline	5162.8 (2339.8 to 18704.1)	10416.9 (5365.9 to 15833.6)		
D-dimer - 48h	8381.3 (7194.4 to 14371)	8381.3 (7194.4 to 14371)		
FDP - Baseline	27941.5 (19700.5 to 47360.8)	22194 (11305.5 to 26289)		
FDP - 48h	33594 (23067.8 to 47656.8)	19257.5 (15305.8 to 24952.3)		
Fibrin monomer - Baseline	75200 (25700 to 118800)	12300 (5100 to 29900)		
Fibrin monomers - 48h	48800 (12000 to 60400)	15200 (4100 to 23200)		

Statistical analyses

Statistical analysis title	Change in D-dimer (baseline to 48h)

Statistical analysis description:

Change in D-dimer from baseline to 48 hours post-randomisation

Comparison groups	PP - Intervention group v PP - Placebo group

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.423 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - Exploratory

[15] - Time x group

Statistical analysis title	Change in FDP (baseline to 48h)

Statistical analysis description:

Change in fibrinogen degradation products (FDP) from baseline to 48 hours post-randomisation

Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.502 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - Exploratory

[17] - Time x group

Statistical analysis title	Change in fibrin monomers (baseline to 48h)

Statistical analysis description:

Change in fibrin monomers from baseline to 48 hours post-randomisation

Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.199 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - Exploratory

[19] - Time x group

Secondary: Mortality (ITT analysis)

End point title	Mortality (ITT analysis)

End point description:

ITT analysis of the number of patients who died at each timepoint in the 2 treatment groups

End point type	Secondary

End point timeframe:

7-, 30- and 90 day mortality

End point values	Iloprost/eptifibatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	9		
Units: Number				
7-day	0	2		
30-day	2	4		
90-day	4	5		

Statistical analyses

Statistical analysis title	7-day mortality
Comparison groups	Iloprost/eptifibatide v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.13
Method	Mixed models analysis

Statistical analysis title	30-day mortality
Comparison groups	Iloprost/eptifibatide v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.15
Method	Mixed models analysis

Statistical analysis title	90-day mortality
Comparison groups	Iloprost/eptifibatide v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.212
Method	Mixed models analysis

Secondary: Mortality (PP analysis)

End point title	Mortality (PP analysis)
End point description:	
Per protocol analysis for mortality	
End point type	Secondary
End point timeframe:	
7- , 30 and 90 day post randomisation	

End point values	PP - Intervention group	PP - Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: Number				
7-days mortality	0	1		
30-day mortality	1	2		
90-day mortality	3	3		

Statistical analyses

Statistical analysis title	7-day mortality
Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.333
Method	Mixed models analysis

Statistical analysis title	30-day mortality
Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.254
Method	Mixed models analysis

Statistical analysis title	90-day mortality
Comparison groups	PP - Intervention group v PP - Placebo group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.294
Method	Mixed models analysis

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:	
From inclusion until day 90 for each patient	
Adverse event reporting additional description:	
Only SAE are recorded according to the protocol	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Experimental arm
Reporting group description:	
Data for all patients included in the intervention arm	
Reporting group title	Placebo arm
Reporting group description:	
Data for all patients included in the placebo arm	

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 SAE are recorded in this trial. This is approved by the regulatory authorities.

Serious adverse events	Experimental arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)	3 / 9 (33.33%)	
number of deaths (all causes)	4	5	
number of deaths resulting from adverse events	2	2	
Vascular disorders			
Thrombosis	Additional description: Thrombosis in the arterial cannula		
subjects affected / exposed	0 / 15 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage	Additional description: Intraabdominal bleeding after liver abscess drainage		
subjects affected / exposed	0 / 15 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haematoma	Additional description: Cerebral incarceration		
subjects affected / exposed	1 / 15 (6.67%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			

Bradycardia	Additional description: Severe bradycardia (<40 mmHg) 4 hours post intervention start. Treated as cardiac arrest.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	Additional description: Respiratory failure 10 days after inclusion		
subjects affected / exposed	1 / 15 (6.67%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure	Additional description: Dead after organ failure, with terminal hepatic failure. Patient has medical history of cirrhosis		
subjects affected / exposed	0 / 15 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Enzyme level increased	Additional description: Cardiac enzymes increasing, suspicion of type II myocardia infract		
subjects affected / exposed	1 / 15 (6.67%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Experimental arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 9 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2015	The amendment allowed to extend the study
16 January 2017	Added measure on extra endothelial biomarkers with metabolomics.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The septic shock definition might have limited the potential effect of the intervention, since not all patients with septic shock have equal degrees of endothelial dysfunction. Also limited power due to the small sample size is a limitation

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31488213