Clinical trial results:
Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU)

Summary

EudraCT number	2015-000318-24
Trial protocol	DK FI NO NL
Global end of trial date	22 October 2018

Results information

Result version number	v1 (current)
This version publication date	02 May 2019
First version publication date	02 May 2019
Summary attachment (see zip file)	main results and paper (2018. Krag_Marker. SUP-ICU.pdf)

Trial information

Trial identification

Sponsor protocol code	RH-ITA-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02467621
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dept. of Intensive Care 4131, Copenhagen University Hospital Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Ass. prof. Morten Hylander Møller, Dept. of Intensive Care 4131, Copenhagen University Hospital Rigshospitalet, 0045 35458685, mortenhylander@gmail.com
Scientific contact	Ass. prof. Morten Hylander Møller, Dept. of Intensive Care 4131, Copenhagen University Hospital Rigshospitalet, 0045 35458685, mortenhylander@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	21 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2018
Global end of trial reached?	Yes
Global end of trial date	22 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess benefits and harms in the use of pantoprazole as stress ulcer prophylaxis in adult critically ill patients.

Protection of trial subjects:

All trial subjects received the highest standard of care with high degree of monitoring.
Also, stress ulcer prophylaxis is an intervention abundantly used across the world.

Background therapy:

All other treatments than the trial drug were at the discretion of the treating clinicians.

Evidence for comparator:

Placebo-controlled trial.

Actual start date of recruitment	04 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 172
Country: Number of subjects enrolled	Norway: 197
Country: Number of subjects enrolled	Denmark: 2125
Country: Number of subjects enrolled	Finland: 258
Country: Number of subjects enrolled	Switzerland: 472
Country: Number of subjects enrolled	United Kingdom: 67
Worldwide total number of subjects	3291
EEA total number of subjects	2819

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)	1389
From 65 to 84 years	1742
85 years and over	160

Subject disposition

Recruitment

Recruitment details:

Recruitment was performed on schedule.

Pre-assignment

Screening details:

Adults (age ≥ 18 years) that were acutely admitted to the ICU and fulfilled one or more of our predefined risk factors for gastrointestinal bleeding were screened

We screened 10.000 patients. 3.350 were randomised. 3291 were analysed (specified in published paper).

Period 1

Period 1 title	Intervention period (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 following persons were blinded: participants, care providers, investigators, outcomes assessors and trial statistician.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pantoprazole, PR1

Arm description:

Pantoprazole 40 mg (daily intravenous injection)

Arm type	Experimental
Investigational medicinal product name	Pantoprazole, PR1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pantoprazole 40 mg milligram(s) administered intravenously once daily until ICU discharge (for a maximum of 90 days).
Preceding administration: 10 mL of isotonic sodium chloride 0.9% (normal saline) added to masked study vial containing pantoprazole powder for solution for injection.

Arm title	Placebo, PL1

Arm description:

Placebo (daily intravenous injection)

Arm type	Placebo
Investigational medicinal product name	Placebo, PL1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Placebo administered intravenously once daily until ICU discharge (for a maximum of 90 days).
Preceding administration: 10 mL of isotonic sodium chloride 0.9% (normal saline) added to masked empty study vial.

Number of subjects in period 1	Pantoprazole, PR1	Placebo, PL1
Started	1644	1647
Completed	1644	1647

Baseline characteristics

Reporting groups	
Reporting group title	Pantoprazole, PR1
Reporting group description: Pantoprazole 40 mg (daily intravenous injection)	

Reporting group title	Placebo, PL1
Reporting group description: Placebo (daily intravenous injection)	

Reporting group values	Pantoprazole, PR1	Placebo, PL1	Total
Number of subjects	1644	1647	3291
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			
3298 started the trial, however we do not report for the 7 patients (1 in pantoprazole group, 6 in the placebo Group) who withdrew consent to the use of data			
Units: years			
median	67	67	
inter-quartile range (Q1-Q3)	56 to 75	55 to 75	-
Gender categorical			
Not recorded: 7 patients not allowing for use of data.			
Units: Subjects			
Female	605	580	1185
Male	1039	1067	2106
Not recorded	0	0	0

End points

End points reporting groups

Reporting group title	Pantoprazole, PR1
Reporting group description: Pantoprazole 40 mg (daily intravenous injection)	

Reporting group title	Placebo, PL1
Reporting group description: Placebo (daily intravenous injection)	

Primary: 90 days all-cause mortality

End point title	90 days all-cause mortality
End point description:	

End point type	Primary
End point timeframe: 90 days from randomisation.	

End point values	Pantoprazole, PR1	Placebo, PL1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1642	1640		
Units: Numbers	510	499		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Analysis adjusted for the stratification variables: trial site and hematological malignancy. 9 patients were lost to 90-day mortality follow-up and were therefore not included in this analysis.	
Comparison groups	Pantoprazole, PR1 v Placebo, PL1
Number of subjects included in analysis	3282
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.76
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.13

Notes:

[1] - RR computed from OR

Secondary: Clinically important events

End point title	Clinically important events

End point description:

Composite outcome consisting of the following elements:
- clinically important gastrointestinal bleeding
- new-onset pneumonia
- clostridium difficile infection
- myocardial ischemia

End point type	Secondary

End point timeframe:

Randomisation until ICU discharge (within a maximum of 90 days from randomisation)

End point values	Pantoprazole, PR1	Placebo, PL1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1644	1647		
Units: Numbers	360	372		

Statistical analyses

Statistical analysis title	primary analysis

Statistical analysis description:

Analysis adjusted for stratification variables: trial site and hematological malignancy

Comparison groups	Placebo, PL1 v Pantoprazole, PR1
Number of subjects included in analysis	3291
Analysis specification	Pre-specified
Analysis type	superiority[2]
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.11

Notes:

[2] - RR computed from OR
P-value not presented for secondary outcomes because of the lack of adjustments for multiple comparisons

Secondary: Clinically important gastrointestinal bleeding

End point title	Clinically important gastrointestinal bleeding

End point description:

Defined as overt gastrointestinal bleeding and at least one of the following four features within 24 hours of gastrointestinal bleeding, in the absence of other causes, in the ICU:
- a spontaneous decrease in systolic blood pressure, mean arterial pressure, or diastolic blood pressure of 20 mm Hg or more
- initiation of treatment with a vasopressor or a 20% increase in vasopressor dose
- a decrease in hemoglobin of at least 2 g per deciliter [1.24 mmol per liter]
- transfusion of two or more units of packed red cells

End point type	Secondary

End point timeframe:

Randomisation until ICU discharge (within a maximum of 90 days from randomisation)

End point values	Pantoprazole, PR1	Placebo, PL1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1644	1647		
Units: Numbers	41	69		

Statistical analyses

Statistical analysis title	primary analysis

Statistical analysis description:

Analysis adjusted for stratification variables: trial site and hematological malignancy

Comparison groups	Pantoprazole, PR1 v Placebo, PL1
Number of subjects included in analysis	3291
Analysis specification	Pre-specified
Analysis type	superiority[3]
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.86

Notes:

[3] - RR computed from OR
P-value not presented for secondary outcomes because of the lack of adjustments for multiple comparisons

Secondary: Infectious adverse events

End point title	Infectious adverse events

End point description:

End point type	Secondary

End point timeframe:

Randomisation until ICU discharge (within a maximum of 90 days from randomisation)

End point values	Pantoprazole, PR1	Placebo, PL1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1644	1647		
Units: Numbers	276	279		

Statistical analyses

Statistical analysis title	primary analysis

Statistical analysis description:

Analysis adjusted for the stratification variables: trial site and hematological malignancy

Comparison groups	Placebo, PL1 v Pantoprazole, PR1
Number of subjects included in analysis	3291
Analysis specification	Pre-specified
Analysis type	superiority[4]
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.16

Notes:

[4] - RR computed from OR
P-value not presented for secondary outcomes because of the lack of adjustments for multiple comparisons

Secondary: Serious adverse reactions

End point title	Serious adverse reactions

End point description:

Severe adverse reactions were defined as:
- anaphylactic reactions*
- agranulocytosis*
- pancytopenia*
- acute hepatic failure*
- the Stevens–Johnson syndrome*
- toxic epidermal necrolysis*
- interstitial nephritis*
- angioedema*

* related to the intervention (as judged by the treating clinicians and investigators)

End point type	Secondary

End point timeframe:

Randomisation until ICU discharge (within a maximum of 90 days from randomisation)

End point values	Pantoprazole, PR1	Placebo, PL1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1644	1647		
Units: Numbers	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive without the use of life support

End point title	Days alive without the use of life support

End point description:

The percentage of days alive without the use of life support was calculated as the number of days without the use of invasive or noninvasive mechanical ventilation, infusion of vasopressor or inotropic agents, or any form of renal-replacement therapy, divided by the number of days alive within the 90-day follow-up period

End point type	Secondary

End point timeframe:

90 days from randomisation

End point values	Pantoprazole, PR1	Placebo, PL1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1644	1647		
Units: Percentage of days				
median (inter-quartile range (Q1-Q3))	92 (60 to 97)	92 (65 to 97)		

Statistical analyses

Statistical analysis title	primary analysis

Statistical analysis description:

Analysis adjusted for trial site

Comparison groups	Pantoprazole, PR1 v Placebo, PL1

Number of subjects included in analysis	3291
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.34 [6]
Method	The van Elteren test

Notes:

[5] - P-value presented as no parameter estimates can be presented for this test.
Please note: the p-value should be interpreted with caution due to lack of adjustments for multiple comparisons

[6] - Please note: the p-value should be interpreted with caution due to lack of adjustments for multiple comparisons

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
During ICU stay (from randomisation until a maximum of 90 days from randomisation)	
Adverse event reporting additional description:	
Serious adverse events were predefined outcome measures in the trial - please see the 'end points'-section of this report. Full description available in the published paper.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

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

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: SAEs were not recorded as one entity, because the majority of ICU patients will experience several SAEs during their critical illness.
The most important SAEs were captured in specific trial outcome measures (incl. in this report - 'end points'-section) .
Patient charts contain daily registrations of clinical data, which can be obtained on request from medical authorities.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2017	Cancellation of the second interim analysis (of 2.500/3.350 included patients). Due to a high patient inclusion rate in the last part of the SUP-ICU trial, the trial Steering Committee, in full agreement with the the Data Monitoring and Safety Committee (DMSC), decided to cancel the second interim analysis (of 2500/3350 included patients) as the results (incl. 90-day follow-up of 2500 patients) would be available only after the inclusion of the last trial patient. A statement paper from the DMSC following the first interim analysis (1675/3350 included patients) supports this decision. The decision was approved by relevant Danish authorities.

Notes:

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/30354950

http://www.ncbi.nlm.nih.gov/pubmed/27093939

http://www.ncbi.nlm.nih.gov/pubmed/28608496