Clinical trial results:
A Double-blind, Randomised, Placebo-controlled, Phase 2b/3 Adaptive Clinical Trial Investigating the Efficacy and Safety of Selepressin as Treatment for Patients with Vasopressor-dependent Septic Shock

Summary

EudraCT number	2014-003973-41
Trial protocol	BE NL FR DK
Global end of trial date	26 February 2018

Results information

Result version number	v1 (current)
This version publication date	08 March 2019
First version publication date	08 March 2019

Trial information

Trial identification

Sponsor protocol code	000133

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02508649
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals A/S
Sponsor organisation address	International PharmaScience Center, Kay Fiskers Plads 11, Copenhagen S, Denmark, 2300
Public contact	Global Clinical Compliance, Ferring pharmaceuticals, DK0-Disclosure@ferring.com
Scientific contact	Global Clinical Compliance, Ferring pharmaceuticals, DK0-Disclosure@ferring.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	26 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2017
Global end of trial reached?	Yes
Global end of trial date	26 February 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of selepressin plus standard care versus placebo plus standard care in the number of vasopressor- and mechanical ventilator-free days (with penalty for mortality) in subjects with vasopressor-dependent septic shock.

Protection of trial subjects:

The trial was performed in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial, in compliance with the approved protocol and its amendments, Good Clinical Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2015
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	Netherlands: 21
Country: Number of subjects enrolled	Belgium: 242
Country: Number of subjects enrolled	Denmark: 213
Country: Number of subjects enrolled	France: 335
Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	868
EEA total number of subjects	811

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)	337
From 65 to 84 years	479
85 years and over	52

Subject disposition

Recruitment

Recruitment details:

A total of 63 sites were authorised to recruit subjects for the trial between July 2015 and August 2017. Eleven of these sites did not recruit any subjects. The trial sites that randomised subjects to the trial were: 11 in Belgium, 5 in Denmark, 17 in France, 5 in the Netherlands, and 14 in the United States of America.

Pre-assignment

Screening details:

A total of 6377 subjects were screened, of which 868 subjects were randomised (585 subjects were allocated to selepressin [three doses] and 283 subjects were allocated to placebo). Up to four dosing regimens of selepressin were planned to be investigated in the trial. However, the highest dosing regimen was not used.

Period 1

Period 1 title	Overall Trial Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Sterile 0.9% sodium chloride solution given as an infusion.

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

Dosage and administration details:

Sterile 0.9% sodium chloride solution given as an infusion.

Arm title	Selepressin 2.5 ng/kg/Min

Arm description:

Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.

Arm type	Experimental
Investigational medicinal product name	Selepressin 2.5 ng/kg/Min
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.

Arm title	Selepressin 3.75 ng/kg/Min

Arm description:

Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.

Arm type	Experimental
Investigational medicinal product name	Selepressin 3.75 ng/kg/Min
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.

Arm title	Selepressin 5.25 ng/kg/Min

Arm description:

Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.

Arm type	Experimental
Investigational medicinal product name	Selepressin 5.25 ng/kg/Min
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.

Arm title	Selepressin Pooled

Arm description:

All selepressin arms pooled together and treated as a single arm.

Arm type	Experimental
Investigational medicinal product name	Selepressin Pooled
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All selepressin arms pooled together and treated as a single arm.

Number of subjects in period 1	Placebo	Selepressin 2.5 ng/kg/Min	Selepressin 3.75 ng/kg/Min
Started	283	197	189
Dosed	266	191	177
Completed	265	184	174
Not completed	18	13	15
Post randomisation screening failure	12	4	9
Physician decision	1	2	1
Consent withdrawn by subject	4	6	5
Lost to follow-up	1	1	-

Number of subjects in period 1	Selepressin 5.25 ng/kg/Min	Selepressin Pooled

Started	199	585
Dosed	194	562
Completed	189	547
Not completed	10	38
Post randomisation screening failure	3	16
Physician decision	-	3
Consent withdrawn by subject	6	17
Lost to follow-up	1	2

Period 2

Period 2 title	Baseline Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a double-blind trial in which the subjects, the investigators and the other trial site staff, the clinical coordinating centres, the trial steering committee, the clinical trial team at Ferring and its representatives were blinded to the treatment assignment.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Sterile 0.9% sodium chloride solution given as an infusion.

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

Dosage and administration details:

Sterile 0.9% sodium chloride solution given as an infusion.

Arm title	Selepressin 2.5 ng/kg/Min

Arm description:

Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.

Arm type	Experimental
Investigational medicinal product name	Selepressin 2.5 ng/kg/Min
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.

Arm title	Selepressin 3.75 ng/kg/Min

Arm description:

Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.

Arm type	Experimental
Investigational medicinal product name	Selepressin 3.75 ng/kg/Min
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.

Arm title	Selepressin 5.25 ng/kg/Min

Arm description:

Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.

Arm type	Experimental
Investigational medicinal product name	Selepressin 5.25 ng/kg/Min
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.

Arm title	Selepressin Pooled

Arm description:

All selepressin arms pooled together and treated as a single arm.

Arm type	Experimental
Investigational medicinal product name	Selepressin Pooled
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All selepressin arms pooled together and treated as a single arm.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 included all subjects that were enrolled in the trial whereas Period 2 included all subjects that were dosed in the trial. Baseline data, efficacy, and safety outcomes are presented for all the dosed subjects.

Number of subjects in period 2	Placebo	Selepressin 2.5 ng/kg/Min	Selepressin 3.75 ng/kg/Min
Started	266	191	177
Completed	263	184	172
Not completed	3	7	5
Consent withdrawn by subject	2	6	5
Lost to follow-up	1	1	-

Number of subjects in period 2	Selepressin 5.25 ng/kg/Min	Selepressin Pooled
Started	194	562

Completed	187	543
Not completed	7	19
Consent withdrawn by subject	6	17
Lost to follow-up	1	2

Baseline characteristics

Reporting groups[1]	
Reporting group title	Placebo
Reporting group description:	
Sterile 0.9% sodium chloride solution given as an infusion.	
Reporting group title	Selepressin 2.5 ng/kg/Min
Reporting group description:	
Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin 3.75 ng/kg/Min
Reporting group description:	
Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin 5.25 ng/kg/Min
Reporting group description:	
Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin Pooled
Reporting group description:	
All selepressin arms pooled together and treated as a single arm.	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Period 1 included all subjects that were enrolled in the trial whereas Period 2 included all subjects that were dosed in the trial. Baseline data, efficacy, and safety outcomes are presented for all the dosed subjects.

Reporting group values	Placebo	Selepressin 2.5 ng/kg/Min	Selepressin 3.75 ng/kg/Min
Number of subjects	266	191	177
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
geometric mean	65.7	66.0	67.2
standard deviation	± 14.56	± 12.76	± 13.13
Gender categorical Units: Subjects			
Female	121	80	70
Male	145	111	107

Ethinicity Units: Subjects			
Hispanic or Latino	4	3	1
Not Hispanic or Latino	262	188	176
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	1	2	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	3	11
White	260	186	161

Reporting group values	Selepressin 5.25 ng/kg/Min	Selepressin Pooled	Total
Number of subjects	194	562	828
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
geometric mean	66.8	66.6	
standard deviation	± 12.47	± 12.76	-
Gender categorical Units: Subjects			
Female	70	220	341
Male	124	342	487
Ethinicity Units: Subjects			
Hispanic or Latino	4	8	12
Not Hispanic or Latino	190	554	816
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	4	11	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	21	25
White	183	530	790

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Sterile 0.9% sodium chloride solution given as an infusion.	
Reporting group title	Selepressin 2.5 ng/kg/Min
Reporting group description:	
Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin 3.75 ng/kg/Min
Reporting group description:	
Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin 5.25 ng/kg/Min
Reporting group description:	
Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin Pooled
Reporting group description:	
All selepressin arms pooled together and treated as a single arm.	

Reporting group title	Placebo
Reporting group description:	
Sterile 0.9% sodium chloride solution given as an infusion.	
Reporting group title	Selepressin 2.5 ng/kg/Min
Reporting group description:	
Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin 3.75 ng/kg/Min
Reporting group description:	
Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin 5.25 ng/kg/Min
Reporting group description:	
Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.	
Reporting group title	Selepressin Pooled
Reporting group description:	
All selepressin arms pooled together and treated as a single arm.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS comprised of all the subjects who were enrolled (i.e. randomised [as planned]) and dosed.	
Subject analysis set title	Selepressin Pooled
Subject analysis set type	Full analysis
Subject analysis set description:	
All selepressin arms pooled together and treated as a single arm.	

Primary: Vasopressor- and Mechanical Ventilator-free Days (PVFDs)

End point title	Vasopressor- and Mechanical Ventilator-free Days (PVFDs)[1]

End point description:

Composite endpoint defined as number of days from start of treatment to 30 days thereafter during which subject is:
1. Alive. However, if patient dies within these 30-days then PVFDs will be zero even if there is a period during which subject is alive and free of both vasopressor treatment and mechanical ventilation;
2. Free of treatment with vasopressors: Less than 60 min during any contiguous 24-h period. If a patient requires vasopressors longer than 60 min in total during any 24-h period, the intervening intervals during which they are free of vasopressors will not be included in the determination of PVFDs;
3. Free of any mechanical ventilation: Less than 60 min during any contiguous 24-h period. If a patient requires mechanical ventilation longer than 60 min in total during any 24-h period, the intervening intervals during which they are not receiving mechanical ventilation will not be included in the period free of mechanical ventilation in the determination of PVFDs.

End point type	Primary

End point timeframe:

Up to Day 30

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis was pre-planned to be performed only on the Placebo arm and the Selepressin Pooled arm, and not for all the arms as detailed in the statistical analysis plan of this trial. Therefore, the results for this endpoint are reported only for these two arms.

End point values	Placebo	Selepressin Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	266	562		
Units: days				
least squares mean (confidence interval 95%)	14.45 (12.82 to 16.09)	15.00 (13.77 to 16.23)		

Statistical analyses

Statistical analysis title	Placebo, Selepressin Pooled

Statistical analysis description:

The primary endpoint was analysed using a van Elteren test. The analysis included a test of superiority using a two-sided 5% significance level.

Comparison groups	Placebo v Selepressin Pooled
Number of subjects included in analysis	828
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3015
Method	van Elteren test
Parameter estimate	Treatment difference
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	2.43

Secondary: All-cause Mortality

End point title	All-cause Mortality[2]

End point description:

Defined as the fraction of subjects that have died, regardless of cause.

End point type	Secondary

End point timeframe:

At Day 90

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis was pre-planned to be performed only on the Placebo arm and the Selepressin Pooled arm, and not for all the arms as detailed in the statistical analysis plan of this trial. Therefore, the results for this endpoint are reported only for these two arms.

End point values	Placebo	Selepressin Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	257	526		
Units: percent				
number (not applicable)	39.44	40.59		

Statistical analyses

Statistical analysis title	Placebo, Selepressin Pooled

Statistical analysis description:

Mortality was analysed using a logistic regression model with the individual sequential organ failure assessment (SOFA) scores and age as covariates and treatment arm as factor.

Comparison groups	Placebo v Selepressin Pooled
Number of subjects included in analysis	783
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.7694
Method	Logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.762
upper limit	1.445

Notes:

[3] - An odds ratio < 1 in proportion of subjects dying indicates lower mortality in the selepressin group.

Secondary: Renal Replacement Therapy (RRT)-free Days

End point title	Renal Replacement Therapy (RRT)-free Days[4]

End point description:

RRT-free days was defined as the number of days a subject is free of treatment with any form of RRT

(continuous RRT, intermittent haemodialysis or peritoneal dialysis) and the intermittent periods were not included.
RRT-free days was analysed excluding subjects on RRT for chronic renal failure at time of randomisation.

End point type	Secondary

End point timeframe:

Up to Day 30

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis was pre-planned to be performed only on the Placebo arm and the Selepressin Pooled arm, and not for all the arms as detailed in the statistical analysis plan of this trial. Therefore, the results for this endpoint are reported only for these two arms.

End point values	Placebo	Selepressin Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	261	550		
Units: days				
least squares mean (confidence interval 95%)	18.21 (16.14 to 20.29)	18.50 (17.03 to 19.98)		

Statistical analyses

Statistical analysis title	Placebo, Selepressin Pooled

Statistical analysis description:

This endpoint was analysed using a van Elteren test. The analysis was a test of superiority using a two-sided 5% significance level.

Comparison groups	Placebo v Selepressin Pooled
Number of subjects included in analysis	811
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8458
Method	van Elteren test
Parameter estimate	Treatment difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	2.65

Secondary: Intensive Care Unit (ICU)-free Days

End point title	Intensive Care Unit (ICU)-free Days[5]

End point description:

The ICU free days, as for the PVFDs, reflect the time from last discharge of the ICU to Day 30 with an absolute penalty for mortality, i.e., any subject that died within this 30-day period was assigned zero value).

End point type	Secondary

End point timeframe:

Up to Day 30

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis was pre-planned to be performed only on the Placebo arm and the Selepressin Pooled arm, and not for all the arms as detailed in the statistical analysis plan of this trial. Therefore, the results for this endpoint are reported only for these two arms.

End point values	Placebo	Selepressin Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	266	562		
Units: days				
least squares mean (confidence interval 95%)	12.15 (10.66 to 13.64)	12.64 (11.51 to 13.76)		

Statistical analyses

Statistical analysis title	Placebo, Selepressin Pooled

Statistical analysis description:

This endpoint was analysed using a van Elteren test. The analysis was a test of superiority using a two-sided
5% significance level.

Comparison groups	Placebo v Selepressin Pooled
Number of subjects included in analysis	828
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4124
Method	van Elteren test
Parameter estimate	Treatment difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	2.19

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) occurring after the investigational medicinal product (IMP) infusion to within 12 hours after the IMP infusion was stopped.

Adverse event reporting additional description:

TEAEs were defined as adverse events that occurred after the IMP infusion to within 12 hours after the IMP infusion was stopped. All treated subjects were included in the safety analysis set and were analysed according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Sterile 0.9% sodium chloride solution given as an infusion.

Reporting group title	Selepressin 2.5 ng/kg/Min

Reporting group description:

Starting dose: 1.7 ng/kg/min selepressin; Maximum dose: 2.5 ng/kg/min selepressin, given as an infusion.

Reporting group title	Selepressin 3.75 ng/kg/Min

Reporting group description:

Starting dose: 2.5 ng/kg/min selepressin; Maximum dose: 3.75 ng/kg/min selepressin, given as an infusion.

Reporting group title	Selepressin 5.25 ng/kg/Min

Reporting group description:

Starting dose: 3.5 ng/kg/min selepressin; Maximum dose: 5.25 ng/kg/min selepressin, given as an infusion.

Serious adverse events	Placebo	Selepressin 2.5 ng/kg/Min	Selepressin 3.75 ng/kg/Min
Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 266 (31.95%)	57 / 191 (29.84%)	65 / 177 (36.72%)
number of deaths (all causes)	58	43	40
number of deaths resulting from adverse events	58	43	40
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			

subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant neoplasm progression			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastatic carcinoma of the bladder			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Distributive shock			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dry gangrene			

subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ischaemia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor peripheral circulation			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	4 / 266 (1.50%)	1 / 191 (0.52%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 4	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 4	0 / 1	1 / 1
Shock haemorrhagic			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombosis			

subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasoconstriction			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 266 (0.38%)	1 / 191 (0.52%)	4 / 177 (2.26%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	24 / 266 (9.02%)	10 / 191 (5.24%)	17 / 177 (9.60%)
occurrences causally related to treatment / all	0 / 24	0 / 10	0 / 17
deaths causally related to treatment / all	0 / 24	0 / 10	0 / 17
Organ failure			

subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	4 / 266 (1.50%)	3 / 191 (1.57%)	3 / 177 (1.69%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Acute respiratory failure			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	2 / 177 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Mediastinal mass			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	3 / 266 (1.13%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Investigations			
Cardiac output decreased			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	0 / 266 (0.00%)	2 / 191 (1.05%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endotracheal intubation complication			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemothorax			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 266 (0.38%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 266 (0.00%)	2 / 191 (1.05%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	3 / 266 (1.13%)	5 / 191 (2.62%)	5 / 177 (2.82%)
occurrences causally related to treatment / all	1 / 3	4 / 7	0 / 6
deaths causally related to treatment / all	1 / 2	1 / 2	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 266 (0.38%)	1 / 191 (0.52%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cyanosis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Defect conduction intraventricular			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Myocardial depression			

subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 266 (0.38%)	1 / 191 (0.52%)	4 / 177 (2.26%)
occurrences causally related to treatment / all	1 / 1	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial stunning			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulseless electrical activity			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	2 / 177 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Supraventricular tachycardia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 266 (0.38%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Coma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	2 / 266 (0.75%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vasculitis cerebral			

subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic necrosis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal compartment syndrome			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colonic fistula			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ischaemia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Ileus			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal ischaemia			
subjects affected / exposed	3 / 266 (1.13%)	4 / 191 (2.09%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	2 / 3	3 / 4	1 / 1
deaths causally related to treatment / all	0 / 1	2 / 3	1 / 1
Large intestine perforation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			

subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic hepatic failure			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gallbladder disorder			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 266 (0.38%)	1 / 191 (0.52%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatocellular injury			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic hepatitis			

subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin discolouration			
subjects affected / exposed	1 / 266 (0.38%)	2 / 191 (1.05%)	2 / 177 (1.13%)
occurrences causally related to treatment / all	1 / 1	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 266 (1.88%)	0 / 191 (0.00%)	2 / 177 (1.13%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 266 (0.38%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fasciitis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Extradural abscess			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia			
subjects affected / exposed	4 / 266 (1.50%)	2 / 191 (1.05%)	2 / 177 (1.13%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	15 / 266 (5.64%)	10 / 191 (5.24%)	12 / 177 (6.78%)
occurrences causally related to treatment / all	1 / 15	0 / 10	0 / 12
deaths causally related to treatment / all	1 / 14	0 / 9	0 / 9
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hyperlactacidaemia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 191 (0.52%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 191 (0.00%)	1 / 177 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Serious adverse events	Selepressin 5.25 ng/kg/Min		
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 194 (29.38%)		
number of deaths (all causes)	42		
number of deaths resulting from adverse events	42		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung cancer metastatic			

subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphoma				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic carcinoma of the bladder				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic neoplasm				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Circulatory collapse				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Distributive shock				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dry gangrene				

subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hypertension			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	3 / 194 (1.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Ischaemia			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Poor peripheral circulation			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock			
subjects affected / exposed	3 / 194 (1.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Shock haemorrhagic			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vasoconstriction				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
General disorders and administration site conditions				
Catheter site haemorrhage				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperthermia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	12 / 194 (6.19%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 12			
Organ failure				

subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspiration			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mediastinal mass			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			

subjects affected / exposed	5 / 194 (2.58%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	1 / 3		
Investigations			
Cardiac output decreased			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Troponin I increased			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Troponin increased			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endotracheal intubation complication			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Traumatic haemothorax			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiogenic shock			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cyanosis			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Defect conduction intraventricular			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial depression			

subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial stunning			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulseless electrical activity			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Right ventricular failure			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			

subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Brain oedema				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebral ischaemia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vasculitis cerebral				

subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haemolysis			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic necrosis			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal compartment syndrome			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colitis ischaemic			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Colonic fistula				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal perforation				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal ischaemia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal necrosis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 2			
Large intestine perforation				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritoneal haemorrhage				

subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic hepatic failure			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gallbladder disorder			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis acute			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular injury			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic hepatitis			

subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin discolouration			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fasciitis			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Arthritis infective			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Device related sepsis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extradural abscess				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Klebsiella sepsis				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Peritonitis bacterial				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 194 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	3 / 194 (1.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Septic shock			
subjects affected / exposed	8 / 194 (4.12%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 7		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperlactacidaemia			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	0 / 194 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Selepressin 2.5 ng/kg/Min	Selepressin 3.75 ng/kg/Min
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 266 (35.34%)	54 / 191 (28.27%)	63 / 177 (35.59%)
Injury, poisoning and procedural complications			
Expired product administered			
subjects affected / exposed	50 / 266 (18.80%)	26 / 191 (13.61%)	29 / 177 (16.38%)
occurrences (all)	94	48	47
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	30 / 266 (11.28%)	22 / 191 (11.52%)	24 / 177 (13.56%)
occurrences (all)	43	23	27

Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 24 / 266 (9.02%) 25 12 / 266 (4.51%) 13	 12 / 191 (6.28%) 13 9 / 191 (4.71%) 9	 6 / 177 (3.39%) 6 10 / 177 (5.65%) 10
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 4 / 266 (1.50%) 4	 5 / 191 (2.62%) 5	 9 / 177 (5.08%) 9

Non-serious adverse events	Selepressin 5.25 ng/kg/Min		
Total subjects affected by non-serious adverse events subjects affected / exposed	 60 / 194 (30.93%)		
Injury, poisoning and procedural complications Expired product administered subjects affected / exposed occurrences (all)	 31 / 194 (15.98%) 62		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	 22 / 194 (11.34%) 29		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 7 / 194 (3.61%) 7 11 / 194 (5.67%) 11		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 4 / 194 (2.06%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2016	This was a substantial amendment, which was implemented during the conduct of the trial. The main reasons for this protocol amendment were to implement the following changes to the protocol: • To allow use of infusion pumps for administration of the investigational medicinal product. • To allow for calcium (free or total), creatinine (plasma or serum), and troponin (I or T) measurements according to local clinical practice. Uric acid was not routinely measured in clinical practice and therefore, uric acid was no longer required to be collected. • To introduce the recording of the highest lactate level obtained in accordance with local clinical practice in the pre-IMP treatment period following start of vasopressor treatment and to clarify that venous lactate could be recorded if arterial lactate had not been measured.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported