



**Clinical trial results:**

**A Randomized, Double-Blind, Placebo-Controlled, Four-Arm, Parallel-Group, Proof of Concept, and Dose-Finding Adaptive Phase 2a/2b Study to Investigate the Safety, Tolerability and Efficacy and Effect on Quality of Life of Human Recombinant Alkaline Phosphatase in the Treatment of Patients With Sepsis-Associated Acute Kidney Injury**

**Summary**

EudraCT number	2014-000761-40
Trial protocol	BE FI CZ AT NL ES IT DE
Global end of trial date	14 August 2017

**Results information**

Result version number	v1 (current)
This version publication date	30 May 2018
First version publication date	30 May 2018

**Trial information**

**Trial identification**

Sponsor protocol code	AP-recAP-AKI-02-01
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02182440
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	AM-Pharma B.V.
Sponsor organisation address	Rumpsterweg 6, AK Bunnik, Netherlands, 3981
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Scientific contact	Jacques Arend, AM-Pharma B.V., +31 30 2289222, j.arend@am-pharma.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	12 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2017
Global end of trial reached?	Yes
Global end of trial date	14 August 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The trial was a randomized, double blind, placebo-controlled, 4 arm parallel-group, proof of concept and dose finding trial. The study consisted of two parts with one interim analysis between the two parts. Part 1 had 4 arms: placebo, 0.4 mg/kg, 0.8 mg/kg or 1.6 mg/kg recombinant recAP and part 2 had two arms by placebo and a chosen concentration of recAP determined during the interim analysis, being 1.6 mg/kg recAP. A minimum of 290 patients suffering sepsis associated acute kidney injury had to be enrolled, 120 patients in part 1 and 170 patients in part 2. Patients were assigned randomly to the different treatment arms in Part 1 and Part 2.

The primary objectives of the trial were:

1. To investigate the effect of recAP on renal function and related clinical parameters in patients with SA-AKI.
2. To determine the therapeutic dose(s) of recAP to support the pivotal Phase 3 program.

Protection of trial subjects:

The trial was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the international Council for Harmonisation ICH E6(R1), US Code of Federal Regulations, and all other applicable regulations.

The informed consent process of unconscious patients was documented and approved by Ethical committee or competent authorities before start of the trial.

Patients consented as soon as they were medically able.

Patients were admitted to ICUs or intermediate care unit with experienced and qualified staff. Patients were closely monitored in terms of vital signs and adverse events. recAP treatment was an add on treatment on the normal routine medical care.

Preparation of the study drug was detailed in the pharmacy manual and the execution was checked by the four eye principle.

Background therapy:

There are currently no pharmacological interventions approved for the treatment of SA-AKI. Only Renal Replacement Therapy is currently used as a supportive treatment option. Only sites were selected for the trial which followed KDIGO guidelines for acute kidney injury as standard of care for Acute kidney injury and the Surviving Sepsis Campaign guidelines for the care of sepsis.

Evidence for comparator:

The study drug is used as an add-on therapy in addition to the routine care for SA-AKI. In order to keep the blinding a placebo arm was introduced.

Actual start date of recruitment	24 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Netherlands: 75

Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Austria: 26
Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Finland: 17
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	301
EEA total number of subjects	274

Notes:

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### 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)	121
From 65 to 84 years	180
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients, female or male aged 18 to 85 years, admitted to the ICU or intermediate care unit with a confirmed sepsis associated acute kidney injury diagnosis. Patients were eligible, when they met all inclusion criteria and none of the exclusion criteria.

### Pre-assignment

Screening details:

Diagnosis of sepsis by SIRS criteria and AKI diagnosis (at least AKIN stage 1) should have been established respectively <96 hr and <72 hr before treatment. Continuation of AKI should be confirmed before randomization. Known CKD patients were excluded.

### Period 1

Period 1 title	Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

For each site a specific blinding plan was put in place. All persons involved in the study were blinded to treatment assignment. The randomization schedule was held by an independent PPD team at a different regional location and was not revealed to the blinded study team until all patients had completed the study and the database had been locked for the end of the study. The investigator could break the blind when a medical emergency occurred.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	recAP, 0.4 mg/kg [250 U/kg]

Arm description:

Patients received 1-hour intravenous (IV) infusion of recAP 0.4 mg/kg [250 U/kg] once daily, for 3 consecutive days.

Arm type	Experimental
Investigational medicinal product name	Recombinant human alkaline phosphatase
Investigational medicinal product code	
Other name	recAP
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-hour intravenous (IV) infusion of recAP 0.4 mg/kg [250 U/kg] once daily, for 3 consecutive days.

<b>Arm title</b>	recAP, 0.8 mg/kg [500 U/kg]
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Arm description:

Patients received 1-hour intravenous (IV) infusion of recAP 0.8 mg/kg [500 U/kg] once daily, for 3 consecutive days.

Arm type	Experimental
Investigational medicinal product name	Recombinant human alkaline phosphatase
Investigational medicinal product code	
Other name	recAP
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-hour intravenous (IV) infusion of recAP 0.8 mg/kg [500 U/kg] once daily, for 3 consecutive days.

<b>Arm title</b>	recAP, 1.6 mg/kg [1000 U/kg]
Arm description: Patients received 1-hour intravenous (IV) infusion of recAP 1.6 mg/kg [1000 U/kg] once daily, for 3 consecutive days.	
Arm type	Experimental
Investigational medicinal product name	Recombinant human alkaline phosphatase
Investigational medicinal product code	
Other name	recAP
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-hour intravenous (IV) infusion of recAP 1.6 mg/kg [1000 U/kg] once daily, for 3 consecutive days.

<b>Arm title</b>	Placebo
Arm description: Patients received 1-hour intravenous (IV) infusion of Placebo once daily, for 3 consecutive days.	
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:

1-hour intravenous (IV) infusion of Placebo once daily, for 3 consecutive days.

<b>Number of subjects in period 1</b>	recAP, 0.4 mg/kg [250 U/kg]	recAP, 0.8 mg/kg [500 U/kg]	recAP, 1.6 mg/kg [1000 U/kg]
Started	39	35	111
Completed	25	24	81
Not completed	14	11	30
Consent withdrawn by subject	1	3	4
Physician decision	-	-	-
Adverse event, non-fatal	1	-	-
Other	3	3	10
Death	8	5	16
Protocol deviation	1	-	-

<b>Number of subjects in period 1</b>	Placebo
Started	116
Completed	71
Not completed	45
Consent withdrawn by subject	1
Physician decision	1
Adverse event, non-fatal	-
Other	12

Death	31
Protocol deviation	-

## Baseline characteristics

### Reporting groups

Reporting group title	recAP, 0.4 mg/kg [250 U/kg]
Reporting group description: Patients received 1-hour intravenous (IV) infusion of recAP 0.4 mg/kg [250 U/kg] once daily, for 3 consecutive days.	
Reporting group title	recAP, 0.8 mg/kg [500 U/kg]
Reporting group description: Patients received 1-hour intravenous (IV) infusion of recAP 0.8 mg/kg [500 U/kg] once daily, for 3 consecutive days.	
Reporting group title	recAP, 1.6 mg/kg [1000 U/kg]
Reporting group description: Patients received 1-hour intravenous (IV) infusion of recAP 1.6 mg/kg [1000 U/kg] once daily, for 3 consecutive days.	
Reporting group title	Placebo
Reporting group description: Patients received 1-hour intravenous (IV) infusion of Placebo once daily, for 3 consecutive days.	

Reporting group values	recAP, 0.4 mg/kg [250 U/kg]	recAP, 0.8 mg/kg [500 U/kg]	recAP, 1.6 mg/kg [1000 U/kg]
Number of subjects	39	35	111
Age categorical Units: Subjects			
Adults <55 years	6	5	23
≥55 to <70 years	18	16	49
≥70 years	15	14	39
Gender categorical Units: Subjects			
Female	11	17	29
Male	28	18	82

Reporting group values	Placebo	Total	
Number of subjects	116	301	
Age categorical Units: Subjects			
Adults <55 years	16	50	
≥55 to <70 years	50	133	
≥70 years	50	118	
Gender categorical Units: Subjects			
Female	32	89	
Male	84	212	

### Subject analysis sets

Subject analysis set title	ITT Combined Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who were randomly assigned to a study drug in either Part 1 or Part 2 of the study,	

excluding patients recruited whilst the interim analysis was performed who were randomly assigned to treatment arms not selected for Part 2.

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<b>Reporting group values</b>	ITT Combined Set		
Number of subjects	290		
Age categorical Units: Subjects			
Adults <55 years	50		
≥55 to <70 years	128		
≥70 years	112		
Gender categorical Units: Subjects			
Female	85		
Male	205		

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## End points

### End points reporting groups

Reporting group title	recAP, 0.4 mg/kg [250 U/kg]
Reporting group description: Patients received 1-hour intravenous (IV) infusion of recAP 0.4 mg/kg [250 U/kg] once daily, for 3 consecutive days.	
Reporting group title	recAP, 0.8 mg/kg [500 U/kg]
Reporting group description: Patients received 1-hour intravenous (IV) infusion of recAP 0.8 mg/kg [500 U/kg] once daily, for 3 consecutive days.	
Reporting group title	recAP, 1.6 mg/kg [1000 U/kg]
Reporting group description: Patients received 1-hour intravenous (IV) infusion of recAP 1.6 mg/kg [1000 U/kg] once daily, for 3 consecutive days.	
Reporting group title	Placebo
Reporting group description: Patients received 1-hour intravenous (IV) infusion of Placebo once daily, for 3 consecutive days.	
Subject analysis set title	ITT Combined Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who were randomly assigned to a study drug in either Part 1 or Part 2 of the study, excluding patients recruited whilst the interim analysis was performed who were randomly assigned to treatment arms not selected for Part 2.	

### Primary: Area under the time-corrected endogenous creatinine clearance curve from Day 1 to Day 7 (AUC1-7)

End point title	Area under the time-corrected endogenous creatinine clearance curve from Day 1 to Day 7 (AUC1-7)
End point description: The primary endpoint is the area under the time-corrected endogenous creatinine clearance curve from Day 1 to Day 7 (AUC 1-7) calculated as the average of the standardized endogenous creatinine clearance value over 7 days.	
End point type	Primary
End point timeframe: Standardized endogenous creatinine clearance is assessed on each day during a 6 +/- 1 hour period and calculated in mL/min as the mean creatinine clearance over the period, which is expected to be representative of the full 24 hours for that day.	

End point values	recAP, 0.4 mg/kg [250 U/kg]	recAP, 0.8 mg/kg [500 U/kg]	recAP, 1.6 mg/kg [1000 U/kg]	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	32	108	106
Units: ml/min				
median (inter-quartile range (Q1-Q3))	46.95 (6.58 to 88.4)	63.45 (8.07 to 96.77)	55.06 (15.01 to 93.88)	45.58 (17.21 to 112.38)

## Statistical analyses

<b>Statistical analysis title</b>	SAP version 3.1, dated 27 Sep 2017
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Statistical analysis description:

The analysis performed on the ITT Part 1 interim set and ITT Part 2 set to determine the difference between placebo and 1.6 mg/kg recAP dosing group was performed by ANOVA on the AUC 1-7 with treatment and site as explanatory variables.

The analysis performed on the ITT combined set to determine the difference between placebo and 1.6 mg/kg recAP dosing group was performed by a combination test based on inverse normal method.

Comparison groups	recAP, 1.6 mg/kg [1000 U/kg] v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.896 <sup>[2]</sup>
Method	Combination test based on inverse normal
Parameter estimate	Difference Least Square means
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Notes:

[1] - For all patients recruited up to the interim analysis, the primary efficacy analysis was conducted for the ITT Combined Set at the interim analysis (which is identical to the ITT Part 1 Interim set) where AUC1-7 was compared between the 3 active treatment groups and placebo.

[2] - ITT Combined - 0.896.

Method ITT Part 1 interim - ANOVA with treatment and site as explanatory variable.

Method ITT Part 2 - ANOVA with treatment and site as explanatory variable.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Investigators were required to report all AEs, regardless of causality, occurring since the informed consent form had been signed until Day 28 after last dose of study drug or later for events possibly, probably, or definitely related to study drug.

Adverse event reporting additional description:

The analysis of the adverse events including the serious adverse events was performed on the safety set. The safety set includes all patients who were randomly assigned and received at least one study drug. The safety set includes 294 patients in total.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	recAP, 0.4 mg/kg
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Reporting group description:

Treatment-emergent AEs were reported for the majority of patients in each of the placebo, 0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg recAP treatment groups, with most treatment-emergent adverse events (TEAEs) in each treatment group being either mild or moderate in severity.

Reporting group title	recAP, 0.8 mg/kg
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Reporting group description:

Treatment-emergent AEs were reported for the majority of patients in each of the placebo, 0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg recAP treatment groups, with most treatment-emergent adverse events (TEAEs) in each treatment group being either mild or moderate in severity.

Reporting group title	recAP, 1.6 mg/kg
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Reporting group description:

Treatment-emergent AEs were reported for the majority of patients in each of the placebo, 0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg recAP treatment groups, with most treatment-emergent adverse events (TEAEs) in each treatment group being either mild or moderate in severity.

Reporting group title	Placebo
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Reporting group description:

Treatment-emergent AEs were reported for the majority of patients in each of the placebo, 0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg recAP treatment groups, with most treatment-emergent adverse events (TEAEs) in each treatment group being either mild or moderate in severity.

<b>Serious adverse events</b>	recAP, 0.4 mg/kg	recAP, 0.8 mg/kg	recAP, 1.6 mg/kg
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	18 / 38 (47.37%)	11 / 35 (31.43%)	47 / 109 (43.12%)
number of deaths (all causes)	10	6	19
number of deaths resulting from adverse events	0	0	0
<b>Vascular disorders</b>			
Shock			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

ARTERIAL HAEMORRHAGE			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIAL INSUFFICIENCY			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
CAPILLARY DISORDER			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
CIRCULATORY COLLAPSE			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
PERIPHERAL ARTERY THROMBOSIS			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SHOCK HAEMORRHAGIC			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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

GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	5 / 109 (4.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 3
Respiratory, thoracic and mediastinal disorders			
Progressive respiratory insufficiency			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
Pneumococcal meningitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
ACUTE LUNG INJURY			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
ACUTE RESPIRATORY FAILURE			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>CHRONIC OBSTRUCTIVE PULMONARY DISEASE</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
<b>EPISTAXIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>HYPOXIA</b>			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PULMONARY CONGESTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PULMONARY EMBOLISM</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PULMONARY HAEMORRHAGE</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>PULMONARY OEDEMA</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>RESPIRATORY ARREST</b>			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>RESPIRATORY DISTRESS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>RESPIRATORY FAILURE</b>			
subjects affected / exposed	4 / 38 (10.53%)	1 / 35 (2.86%)	4 / 109 (3.67%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>ACUTE MYOCARDIAL INFARCTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>Psychiatric disorders</b>			
<b>CONFUSIONAL STATE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Investigations</b>			
<b>ELECTROCARDIOGRAM QT PROLONGED</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>GENERAL PHYSICAL CONDITION ABNORMAL</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Injury, poisoning and procedural complications</b>			
<b>ABDOMINAL WOUND DEHISCENCE</b>			

subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>ANASTOMOTIC LEAK</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>INTESTINAL ANASTOMOSIS COMPLICATION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>POST PROCEDURAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	0 / 109 (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
<b>PROCEDURAL COMPLICATION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>WOUND NECROSIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
<b>Cardiac disorders</b>			
Cardiac failure congestive			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
Asystole with electromechanical dissociation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>ATRIAL FIBRILLATION</b>			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>CARDIAC ARREST</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	4 / 109 (3.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
<b>CARDIAC FAILURE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>CARDIAC FAILURE ACUTE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>CARDIO-RESPIRATORY ARREST</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
<b>CARDIOGENIC SHOCK</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>CARDIOVASCULAR INSUFFICIENCY</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>MYOCARDIAL INFARCTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>SUPRAVENTRICULAR TACHYCARDIA</b>			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>VENTRICULAR FIBRILLATION</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
<b>VENTRICULAR TACHYCARDIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>Nervous system disorders</b>			
<b>CEREBRAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>CEREBROVASCULAR ACCIDENT</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
<b>DEPRESSED LEVEL OF CONSCIOUSNESS</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>HAEMORRHAGE INTRACRANIAL</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>ISCHAEMIC STROKE</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
<b>METABOLIC ENCEPHALOPATHY</b>			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>NEUROMYOPATHY</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>SEDATION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>SUBARACHNOID HAEMORRHAGE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Blood and lymphatic system disorders</b>			
<b>ANAEMIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>DISSEMINATED INTRAVASCULAR COAGULATION</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>THROMBOCYTOPENIA</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Ear and labyrinth disorders</b>			
<b>DEAFNESS UNILATERAL</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Intestinal haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
Bowel obstruction			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
Bowel necrosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
GIT bleeding			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ACUTE ABDOMEN			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ASCITES			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC PSEUDO-OBSTRUCTION			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
DUODENAL PERFORATION			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC FISTULA			

subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
<b>GASTRIC ULCER HAEMORRHAGE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>GASTROINTESTINAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>ILEUS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>INCARCERATED INGUINAL HERNIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>INTESTINAL INFARCTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>INTESTINAL ISCHAEMIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>INTESTINAL OBSTRUCTION</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>INTESTINAL PERFORATION</b>			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>INTRA-ABDOMINAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 109 (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
<b>ISCHAEMIC ENTERITIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>LARGE INTESTINAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>LARGE INTESTINE PERFORATION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>MESENTERIC VEIN THROMBOSIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>RECTAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>UPPER GASTROINTESTINAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>Hepatobiliary disorders</b>			
<b>CHOLESTASIS</b>			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>GALLBLADDER PERFORATION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>HEPATIC FAILURE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>HEPATIC HAEMATOMA</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>HEPATORENAL SYNDROME</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>Skin and subcutaneous tissue disorders</b>			
<b>SKIN NECROSIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal and urinary disorders</b>			
<b>ACUTE KIDNEY INJURY</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>RENAL FAILURE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>Musculoskeletal and connective tissue</b>			

disorders			
<b>FASCIITIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>Infections and infestations</b>			
<b>Nosocomial infection</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>Sepsis</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
<b>Septic with respiratory failure</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>ABDOMINAL ABSCESS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>ABDOMINAL SEPSIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>ABSCCESS INTESTINAL</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BRONCHOPULMONARY ASPERGILLOSIS</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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

<b>CANDIDA INFECTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>CHOLECYSTITIS INFECTIVE</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>CLOSTRIDIUM DIFFICILE INFECTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>GASTROENTERITIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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
<b>IATROGENIC INFECTION</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>INFECTIOUS PLEURAL EFFUSION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>LOWER RESPIRATORY TRACT INFECTION</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>LUNG ABSCESS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>NECROTISING FASCIITIS</b>			

subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>NECROTISING SOFT TISSUE INFECTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PERITONEAL ABSCESS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PERITONITIS</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PHARYNGEAL ABSCESS</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PNEUMONIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	4 / 109 (3.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
<b>PNEUMONIA HERPES VIRAL</b>			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 109 (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
<b>POSTOPERATIVE WOUND INFECTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>SEPTIC SHOCK</b>			

subjects affected / exposed	2 / 38 (5.26%)	4 / 35 (11.43%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 3
<b>SOFT TISSUE INFECTION</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Metabolism and nutrition disorders</b>			
<b>Failure to thrive</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>CACHEXIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	0 / 109 (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

<b>Serious adverse events</b>	Placebo		
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	56 / 112 (50.00%)		
number of deaths (all causes)	33		
number of deaths resulting from adverse events	0		
<b>Vascular disorders</b>			
<b>Shock</b>			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
<b>ARTERIAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>ARTERIAL INSUFFICIENCY</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

CAPILLARY DISORDER				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CIRCULATORY COLLAPSE				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PERIPHERAL ARTERY THROMBOSIS				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PERIPHERAL ISCHAEMIA				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SHOCK HAEMORRHAGIC				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
ASTHENIA				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
MULTIPLE ORGAN DYSFUNCTION SYNDROME				

subjects affected / exposed	7 / 112 (6.25%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 7		
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Progressive respiratory insufficiency</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Pneumococcal meningitis</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>ACUTE LUNG INJURY</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>ACUTE PULMONARY OEDEMA</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>ACUTE RESPIRATORY DISTRESS SYNDROME</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>ACUTE RESPIRATORY FAILURE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>CHRONIC OBSTRUCTIVE PULMONARY DISEASE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

EPISTAXIS				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HYPOXIA				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PULMONARY CONGESTION				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PULMONARY HAEMORRHAGE				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PULMONARY OEDEMA				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY ARREST				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY DISTRESS				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY FAILURE				

subjects affected / exposed	10 / 112 (8.93%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 4		
<b>ACUTE MYOCARDIAL INFARCTION</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Psychiatric disorders</b>			
<b>CONFUSIONAL STATE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Investigations</b>			
<b>ELECTROCARDIOGRAM QT PROLONGED</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>GENERAL PHYSICAL CONDITION ABNORMAL</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Injury, poisoning and procedural complications</b>			
<b>ABDOMINAL WOUND DEHISCENCE</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>ANASTOMOTIC LEAK</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>INTESTINAL ANASTOMOSIS COMPLICATION</b>			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>POST PROCEDURAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>PROCEDURAL COMPLICATION</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>WOUND NECROSIS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
<b>Cardiac failure congestive</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Asystole with electromechanical dissociation</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>ATRIAL FIBRILLATION</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>CARDIAC ARREST</b>			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
<b>CARDIAC FAILURE</b>			

subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
<b>CARDIAC FAILURE ACUTE</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>CARDIO-RESPIRATORY ARREST</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>CARDIOGENIC SHOCK</b>			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>CARDIOVASCULAR INSUFFICIENCY</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>MYOCARDIAL INFARCTION</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>SUPRAVENTRICULAR TACHYCARDIA</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>VENTRICULAR FIBRILLATION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>VENTRICULAR TACHYCARDIA</b>			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Nervous system disorders</b>			
<b>CEREBRAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>CEREBROVASCULAR ACCIDENT</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>DEPRESSED LEVEL OF CONSCIOUSNESS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>HAEMORRHAGE INTRACRANIAL</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>ISCHAEMIC STROKE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>METABOLIC ENCEPHALOPATHY</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>NEUROMYOPATHY</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>SEDATION</b>			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>SUBARACHNOID HAEMORRHAGE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Blood and lymphatic system disorders</b>			
<b>ANAEMIA</b>			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>DISSEMINATED INTRAVASCULAR COAGULATION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>THROMBOCYTOPENIA</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Ear and labyrinth disorders</b>			
<b>DEAFNESS UNILATERAL</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders</b>			
<b>Intestinal haemorrhage</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Bowel obstruction</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Bowel necrosis				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GIT bleeding				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ACUTE ABDOMEN				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ASCITES				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COLONIC PSEUDO-OBSTRUCTION				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DUODENAL PERFORATION				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTRIC FISTULA				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTRIC ULCER HAEMORRHAGE				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL HAEMORRHAGE				

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>ILEUS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>INCARCERATED INGUINAL HERNIA</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>INTESTINAL INFARCTION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>INTESTINAL ISCHAEMIA</b>			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
<b>INTESTINAL OBSTRUCTION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>INTESTINAL PERFORATION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>INTRA-ABDOMINAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>ISCHAEMIC ENTERITIS</b>			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>LARGE INTESTINAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>LARGE INTESTINE PERFORATION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>MESENTERIC VEIN THROMBOSIS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>RECTAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>UPPER GASTROINTESTINAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Hepatobiliary disorders</b>			
<b>CHOLESTASIS</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>GALLBLADDER PERFORATION</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>HEPATIC FAILURE</b>			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>HEPATIC HAEMATOMA</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>HEPATORENAL SYNDROME</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Skin and subcutaneous tissue disorders</b>			
<b>SKIN NECROSIS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			
<b>ACUTE KIDNEY INJURY</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>RENAL FAILURE</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Musculoskeletal and connective tissue disorders</b>			
<b>FASCIITIS</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>Nosocomial infection</b>			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Sepsis</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Septic with respiratory failure</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>ABDOMINAL ABSCESS</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>ABDOMINAL SEPSIS</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>ABSCCESS INTESTINAL</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>BRONCHOPULMONARY ASPERGILLOSIS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>CANDIDA INFECTION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>CHOLECYSTITIS INFECTIVE</b>			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>CLOSTRIDIUM DIFFICILE INFECTION</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>GASTROENTERITIS</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>IATROGENIC INFECTION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>INFECTIOUS PLEURAL EFFUSION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>LOWER RESPIRATORY TRACT INFECTION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>LUNG ABSCESS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>NECROTISING FASCIITIS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>NECROTISING SOFT TISSUE INFECTION</b>			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>PERITONEAL ABSCESS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>PERITONITIS</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>PHARYNGEAL ABSCESS</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>PNEUMONIA</b>			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
<b>PNEUMONIA HERPES VIRAL</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>POSTOPERATIVE WOUND INFECTION</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>SEPTIC SHOCK</b>			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 8		
<b>SOFT TISSUE INFECTION</b>			

subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Metabolism and nutrition disorders</b>			
<b>Failure to thrive</b>			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>CACHEXIA</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	recAP, 0.4 mg/kg	recAP, 0.8 mg/kg	recAP, 1.6 mg/kg
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	35 / 38 (92.11%)	31 / 35 (88.57%)	103 / 109 (94.50%)
<b>Vascular disorders</b>			
<b>HAEMATOMA</b>			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	2 / 109 (1.83%)
occurrences (all)	1	2	2
<b>HYPERTENSION</b>			
subjects affected / exposed	2 / 38 (5.26%)	6 / 35 (17.14%)	14 / 109 (12.84%)
occurrences (all)	2	6	14
<b>HYPOTENSION</b>			
subjects affected / exposed	5 / 38 (13.16%)	2 / 35 (5.71%)	6 / 109 (5.50%)
occurrences (all)	5	2	6
<b>PHLEBITIS</b>			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	2 / 109 (1.83%)
occurrences (all)	1	2	2
<b>General disorders and administration site conditions</b>			
<b>GENERALISED OEDEMA</b>			
subjects affected / exposed	3 / 38 (7.89%)	2 / 35 (5.71%)	9 / 109 (8.26%)
occurrences (all)	3	2	9

MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	5 / 109 (4.59%)
occurrences (all)	2	0	5
OEDEMA PERIPHERAL			
subjects affected / exposed	4 / 38 (10.53%)	5 / 35 (14.29%)	21 / 109 (19.27%)
occurrences (all)	4	5	21
PAIN			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	1 / 109 (0.92%)
occurrences (all)	0	2	1
PYREXIA			
subjects affected / exposed	2 / 38 (5.26%)	3 / 35 (8.57%)	10 / 109 (9.17%)
occurrences (all)	2	3	10
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	6 / 109 (5.50%)
occurrences (all)	1	1	6
DYSPNOEA			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 109 (0.92%)
occurrences (all)	0	1	1
EPISTAXIS			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	2 / 109 (1.83%)
occurrences (all)	1	2	2
HYPOXIA			
subjects affected / exposed	3 / 38 (7.89%)	1 / 35 (2.86%)	1 / 109 (0.92%)
occurrences (all)	3	1	1
LUNG INFILTRATION			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	0 / 109 (0.00%)
occurrences (all)	0	2	0
PLEURAL EFFUSION			
subjects affected / exposed	3 / 38 (7.89%)	4 / 35 (11.43%)	14 / 109 (12.84%)
occurrences (all)	3	4	14
PULMONARY OEDEMA			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	3 / 109 (2.75%)
occurrences (all)	1	1	3
RESPIRATORY FAILURE			

subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5	1 / 35 (2.86%) 1	10 / 109 (9.17%) 10
<b>TACHYPNOEA</b> subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 35 (0.00%) 0	0 / 109 (0.00%) 0
<b>WHEEZING</b> subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 35 (5.71%) 2	0 / 109 (0.00%) 0
<b>Psychiatric disorders</b> <b>AGITATION</b> subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 35 (5.71%) 2	13 / 109 (11.93%) 13
<b>ANXIETY</b> subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	2 / 35 (5.71%) 2	3 / 109 (2.75%) 3
<b>CONFUSIONAL STATE</b> subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	3 / 35 (8.57%) 3	7 / 109 (6.42%) 7
<b>DELIRIUM</b> subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5	5 / 35 (14.29%) 5	14 / 109 (12.84%) 14
<b>DISORIENTATION</b> subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	1 / 35 (2.86%) 1	2 / 109 (1.83%) 2
<b>INSOMNIA</b> subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 35 (5.71%) 2	13 / 109 (11.93%) 13
<b>Investigations</b> <b>BLOOD PHOSPHORUS DECREASED</b> subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 35 (2.86%) 1	3 / 109 (2.75%) 3
<b>BLOOD POTASSIUM DECREASED</b> subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 35 (5.71%) 2	2 / 109 (1.83%) 2
<b>BREATH SOUNDS ABNORMAL</b>			

subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 35 (5.71%) 2	1 / 109 (0.92%) 1
CARDIAC MURMUR subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 35 (5.71%) 2	0 / 109 (0.00%) 0
HAEMOGLOBIN DECREASED subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 35 (2.86%) 1	8 / 109 (7.34%) 8
Injury, poisoning and procedural complications			
ABDOMINAL WOUND DEHISCENCE subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	0 / 35 (0.00%) 0	3 / 109 (2.75%) 3
GASTROINTESTINAL ANASTOMOTIC LEAK subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 35 (5.71%) 2	1 / 109 (0.92%) 1
WOUND DEHISCENCE subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 35 (5.71%) 2	3 / 109 (2.75%) 3
Cardiac disorders			
ATRIAL FIBRILLATION subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6	3 / 35 (8.57%) 3	28 / 109 (25.69%) 28
ATRIAL FLUTTER subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 35 (5.71%) 2	3 / 109 (2.75%) 3
BRADYCARDIA subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 35 (0.00%) 0	1 / 109 (0.92%) 1
CARDIAC FAILURE subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 35 (2.86%) 1	2 / 109 (1.83%) 2
SINUS TACHYCARDIA subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 35 (0.00%) 0	7 / 109 (6.42%) 7
SUPRAVENTRICULAR TACHYCARDIA			

subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	3 / 35 (8.57%) 3	1 / 109 (0.92%) 1
<b>Nervous system disorders</b>			
<b>HEADACHE</b>			
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 35 (5.71%) 2	1 / 109 (0.92%) 1
<b>INTENSIVE CARE UNIT ACQUIRED WEAKNESS</b>			
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 35 (5.71%) 2	5 / 109 (4.59%) 5
<b>Blood and lymphatic system disorders</b>			
<b>ANAEMIA</b>			
subjects affected / exposed occurrences (all)	8 / 38 (21.05%) 8	3 / 35 (8.57%) 3	11 / 109 (10.09%) 11
<b>THROMBOCYTOPENIA</b>			
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 35 (2.86%) 1	8 / 109 (7.34%) 8
<b>THROMBOCYTOSIS</b>			
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	3 / 35 (8.57%) 3	3 / 109 (2.75%) 3
<b>Gastrointestinal disorders</b>			
<b>ABDOMINAL PAIN</b>			
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	3 / 35 (8.57%) 3	3 / 109 (2.75%) 3
<b>CONSTIPATION</b>			
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	3 / 35 (8.57%) 3	12 / 109 (11.01%) 12
<b>DIARRHOEA</b>			
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	3 / 35 (8.57%) 3	16 / 109 (14.68%) 16
<b>GASTROINTESTINAL HAEMORRHAGE</b>			
subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 4	0 / 35 (0.00%) 0	1 / 109 (0.92%) 1
<b>ILEUS PARALYTIC</b>			
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	7 / 109 (6.42%) 7
<b>IMPAIRED GASTRIC EMPTYING</b>			

subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 35 (5.71%) 2	8 / 109 (7.34%) 8
NAUSEA subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 4	3 / 35 (8.57%) 3	13 / 109 (11.93%) 13
RECTAL HAEMORRHAGE subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 35 (5.71%) 2	3 / 109 (2.75%) 3
VOMITING subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	1 / 35 (2.86%) 1	6 / 109 (5.50%) 6
ABDOMINAL DISTENSION subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 35 (5.71%) 2	4 / 109 (3.67%) 4
Skin and subcutaneous tissue disorders			
DECUBITUS ULCER subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 35 (2.86%) 1	9 / 109 (8.26%) 9
ERYTHEMA subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 35 (5.71%) 2	1 / 109 (0.92%) 1
SKIN DISCOLOURATION subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 35 (0.00%) 0	0 / 109 (0.00%) 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	0 / 35 (0.00%) 0	3 / 109 (2.75%) 3
Infections and infestations			
ABDOMINAL ABSCESS subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	3 / 35 (8.57%) 3	3 / 109 (2.75%) 3
CANDIDA INFECTION subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 35 (5.71%) 2	10 / 109 (9.17%) 10
CELLULITIS			

subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 109 (0.00%)
occurrences (all)	2	0	0
<b>FUNGAL INFECTION</b>			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences (all)	2	0	1
<b>HERPES SIMPLEX</b>			
subjects affected / exposed	3 / 38 (7.89%)	0 / 35 (0.00%)	1 / 109 (0.92%)
occurrences (all)	3	0	1
<b>ORAL HERPES</b>			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	3 / 109 (2.75%)
occurrences (all)	1	2	3
<b>PNEUMONIA</b>			
subjects affected / exposed	4 / 38 (10.53%)	2 / 35 (5.71%)	13 / 109 (11.93%)
occurrences (all)	4	2	13
<b>SEPTIC SHOCK</b>			
subjects affected / exposed	2 / 38 (5.26%)	4 / 35 (11.43%)	5 / 109 (4.59%)
occurrences (all)	2	4	5
<b>Metabolism and nutrition disorders</b>			
<b>HYPERGLYCAEMIA</b>			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	7 / 109 (6.42%)
occurrences (all)	2	1	7
<b>HYPERKALAEMIA</b>			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	6 / 109 (5.50%)
occurrences (all)	2	0	6
<b>HYPERNATRAEMIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	6 / 109 (5.50%)
occurrences (all)	0	1	6
<b>HYPOALBUMINAEMIA</b>			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	2 / 109 (1.83%)
occurrences (all)	0	2	2
<b>HYPOGLYCAEMIA</b>			
subjects affected / exposed	3 / 38 (7.89%)	3 / 35 (8.57%)	9 / 109 (8.26%)
occurrences (all)	3	3	9
<b>HYPOKALAEMIA</b>			
subjects affected / exposed	5 / 38 (13.16%)	3 / 35 (8.57%)	14 / 109 (12.84%)
occurrences (all)	5	3	14

HYPOMAGNESAEMIA			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	2 / 109 (1.83%)
occurrences (all)	2	0	2
HYPONATRAEMIA			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	3 / 109 (2.75%)
occurrences (all)	0	2	3
HYPOPHOSPHATAEMIA			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	6 / 109 (5.50%)
occurrences (all)	2	1	6
METABOLIC ACIDOSIS			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	3 / 109 (2.75%)
occurrences (all)	0	2	3
METABOLIC ALKALOSIS			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	3 / 109 (2.75%)
occurrences (all)	0	2	3

<b>Non-serious adverse events</b>	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 112 (99.11%)		
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
HYPERTENSION			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	10		
HYPOTENSION			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	10		
PHLEBITIS			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
General disorders and administration site conditions			
GENERALISED OEDEMA			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
MULTIPLE ORGAN DYSFUNCTION			

SYNDROME			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	7		
OEDEMA PERIPHERAL			
subjects affected / exposed	17 / 112 (15.18%)		
occurrences (all)	17		
PAIN			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
PYREXIA			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
DYSPNOEA			
subjects affected / exposed	8 / 112 (7.14%)		
occurrences (all)	8		
EPISTAXIS			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
HYPOXIA			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
LUNG INFILTRATION			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
PLEURAL EFFUSION			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	11		
PULMONARY OEDEMA			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	7		
RESPIRATORY FAILURE			

subjects affected / exposed occurrences (all)	15 / 112 (13.39%) 15		
TACHYPNOEA subjects affected / exposed occurrences (all)	0 / 112 (0.00%) 0		
WHEEZING subjects affected / exposed occurrences (all)	0 / 112 (0.00%) 0		
Psychiatric disorders AGITATION subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 6		
ANXIETY subjects affected / exposed occurrences (all)	3 / 112 (2.68%) 3		
CONFUSIONAL STATE subjects affected / exposed occurrences (all)	5 / 112 (4.46%) 5		
DELIRIUM subjects affected / exposed occurrences (all)	20 / 112 (17.86%) 20		
DISORIENTATION subjects affected / exposed occurrences (all)	0 / 112 (0.00%) 0		
INSOMNIA subjects affected / exposed occurrences (all)	10 / 112 (8.93%) 10		
Investigations BLOOD PHOSPHORUS DECREASED subjects affected / exposed occurrences (all)	2 / 112 (1.79%) 2		
BLOOD POTASSIUM DECREASED subjects affected / exposed occurrences (all)	2 / 112 (1.79%) 2		
BREATH SOUNDS ABNORMAL			

<p>subjects affected / exposed occurrences (all)</p> <p>CARDIAC MURMUR subjects affected / exposed occurrences (all)</p> <p>HAEMOGLOBIN DECREASED subjects affected / exposed occurrences (all)</p>	<p>0 / 112 (0.00%) 0</p> <p>1 / 112 (0.89%) 1</p> <p>9 / 112 (8.04%) 9</p>		
<p>Injury, poisoning and procedural complications</p> <p>ABDOMINAL WOUND DEHISCENCE subjects affected / exposed occurrences (all)</p> <p>GASTROINTESTINAL ANASTOMOTIC LEAK subjects affected / exposed occurrences (all)</p> <p>WOUND DEHISCENCE subjects affected / exposed occurrences (all)</p>	<p>1 / 112 (0.89%) 1</p> <p>0 / 112 (0.00%) 0</p> <p>0 / 112 (0.00%) 0</p>		
<p>Cardiac disorders</p> <p>ATRIAL FIBRILLATION subjects affected / exposed occurrences (all)</p> <p>ATRIAL FLUTTER subjects affected / exposed occurrences (all)</p> <p>BRADYCARDIA subjects affected / exposed occurrences (all)</p> <p>CARDIAC FAILURE subjects affected / exposed occurrences (all)</p> <p>SINUS TACHYCARDIA subjects affected / exposed occurrences (all)</p> <p>SUPRAVENTRICULAR TACHYCARDIA</p>	<p>25 / 112 (22.32%) 25</p> <p>1 / 112 (0.89%) 1</p> <p>3 / 112 (2.68%) 3</p> <p>6 / 112 (5.36%) 6</p> <p>5 / 112 (4.46%) 5</p>		

subjects affected / exposed occurrences (all)	2 / 112 (1.79%) 2		
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	5 / 112 (4.46%) 5		
INTENSIVE CARE UNIT ACQUIRED WEAKNESS subjects affected / exposed occurrences (all)	4 / 112 (3.57%) 4		
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	15 / 112 (13.39%) 15		
THROMBOCYTOPENIA subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 6		
THROMBOCYTOSIS subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1		
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all)	9 / 112 (8.04%) 9		
CONSTIPATION subjects affected / exposed occurrences (all)	13 / 112 (11.61%) 13		
DIARRHOEA subjects affected / exposed occurrences (all)	12 / 112 (10.71%) 12		
GASTROINTESTINAL HAEMORRHAGE subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1		
ILEUS PARALYTIC subjects affected / exposed occurrences (all)	0 / 112 (0.00%) 0		
IMPAIRED GASTRIC EMPTYING			

subjects affected / exposed occurrences (all)	8 / 112 (7.14%) 8		
NAUSEA subjects affected / exposed occurrences (all)	14 / 112 (12.50%) 14		
RECTAL HAEMORRHAGE subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1		
VOMITING subjects affected / exposed occurrences (all)	5 / 112 (4.46%) 5		
ABDOMINAL DISTENSION subjects affected / exposed occurrences (all)	4 / 112 (3.57%) 4		
Skin and subcutaneous tissue disorders			
DECUBITUS ULCER subjects affected / exposed occurrences (all)	2 / 112 (1.79%) 2		
ERYTHEMA subjects affected / exposed occurrences (all)	3 / 112 (2.68%) 3		
SKIN DISCOLOURATION subjects affected / exposed occurrences (all)	0 / 112 (0.00%) 0		
Renal and urinary disorders			
ACUTE KIDNEY INJURY subjects affected / exposed occurrences (all)	2 / 112 (1.79%) 2		
Infections and infestations			
ABDOMINAL ABSCESS subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1		
CANDIDA INFECTION subjects affected / exposed occurrences (all)	3 / 112 (2.68%) 3		
CELLULITIS			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
<b>FUNGAL INFECTION</b>			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
<b>HERPES SIMPLEX</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
<b>ORAL HERPES</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
<b>PNEUMONIA</b>			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	11		
<b>SEPTIC SHOCK</b>			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	11		
<b>Metabolism and nutrition disorders</b>			
<b>HYPERGLYCAEMIA</b>			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
<b>HYPERKALAEMIA</b>			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
<b>HYPERNATRAEMIA</b>			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	10		
<b>HYPOALBUMINAEMIA</b>			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
<b>HYPOGLYCAEMIA</b>			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
<b>HYPOKALAEMIA</b>			
subjects affected / exposed	17 / 112 (15.18%)		
occurrences (all)	17		

HYPOMAGNESAEMIA			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences (all)	4		
HYPONATRAEMIA			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
HYPOPHOSPATAEMIA			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences (all)	4		
METABOLIC ACIDOSIS			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
METABOLIC ALKALOSIS			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2014	<p>The following is a summary of the major changes implemented with Protocol Amendment 1 version 2.0:</p> <ul style="list-style-type: none"><li>• The IND number was added to the protocol.</li><li>• Study design section was amended in regard to inclusion and exclusion criteria.</li><li>• Safety reporting requirements in Protocol Section 6.3 and Protocol Sections 6.3.14 to 6.5 (inclusive) were amended in the study protocol and all exemptions to AE or serious adverse event (SAE) reporting were removed.</li><li>• The following changes to vital sign measurements were implemented: 1) Vital sign monitoring requirements were amended to include at least hourly monitoring up to 6 hours after the start of infusion of study drug on Day 1; 2) Oxygen saturation was added to the vital sign assessments; 3) It was specified that blood pressure was monitored non-invasively, or invasively via arterial line in patients who already had an arterial line placed as part of standard of care.</li><li>• Accumulating safety and efficacy data during Part 1 of the study were reviewed periodically and ad hoc by the DMC as described in the DMC charter, in addition to the already mentioned DMC role of selecting dose.</li><li>• The definition of the primary endpoint was amended from creatinine clearance to AUC1-7. The formula for calculation of the AUC1-7 was amended to indicate that this was the average of the standardized endogenous creatinine clearance values over the 7 days.</li></ul>
03 February 2016	<p>The following is a summary of the major changes implemented with Protocol Amendment 2 version 3.0:</p> <ul style="list-style-type: none"><li>• Addition of new countries and sites and inclusion of text on analysis of patients during interim analysis period.</li><li>• Study design section had been amended with regard to inclusion and exclusion criteria and end of study was defined as Day 28.</li><li>• Pharmacokinetic assessments were amended to reflect the subset of patients in whom they were performed.</li><li>• Recording of concomitant medication use in the electronic case report form (eCRF) was amended to introduce use of mean dosing by the system.</li><li>• Addition of height for calculation of the body mass index (BMI).</li><li>• Clarification in weight for calculation of study drug dose and treatment administered.</li><li>• Addition of a new analysis set (ITT Part 1 Interim Set). Addition of other analysis sets to reflect the current statistical analysis plan (SAP).</li><li>• Change in cut-off date for capture of unrelated AEs and SAEs.</li><li>• Update to data to be reviewed by DMC.</li><li>• Address was updated for PPD Medical Monitor in European Union.</li><li>• References to para-aminohippuric acid were deleted as it was commercially not available anymore.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported