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

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
Public contact	Jacques Arend, AM-Pharma B.V., +31 30 2289222, j.arend@am-pharma.com
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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	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:

General information about the trial

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 Campain 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:

Population of trial subjects

Subjects enrolled per country

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:

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
Arm title	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.

Arm title	recAP, 0.8 mg/kg [500 U/kg]

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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	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	-	-

Number of subjects in period 1	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.

Reporting group values	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		

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

Statistical analysis title	SAP version 3.1, dated 27 Sep 2017

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[1]
P-value	= 0.896 [2]
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

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	recAP, 0.4 mg/kg

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

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

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

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.

Serious adverse events	recAP, 0.4 mg/kg	recAP, 0.8 mg/kg	recAP, 1.6 mg/kg
Total subjects affected by serious adverse events			
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
Vascular disorders			
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
Pneumococcen 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
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
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
EPISTAXIS			
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
HYPOXIA			
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
PULMONARY CONGESTION			
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
PULMONARY EMBOLISM			
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
PULMONARY 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 / 0	0 / 0	0 / 0
PULMONARY OEDEMA			
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
RESPIRATORY ARREST			

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
RESPIRATORY DISTRESS			
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
RESPIRATORY FAILURE			
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
ACUTE MYOCARDIAL INFARCTION			
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
Psychiatric disorders			
CONFUSIONAL STATE			
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
Investigations			
ELECTROCARDIOGRAM QT PROLONGED			
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 CONDITION ABNORMAL			
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
Injury, poisoning and procedural complications			
ABDOMINAL WOUND DEHISCENCE			

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
ANASTOMOTIC LEAK			
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
INTESTINAL ANASTOMOSIS COMPLICATION			
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
POST PROCEDURAL HAEMORRHAGE			
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
PROCEDURAL COMPLICATION			
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
WOUND 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 / 0	0 / 0
Cardiac disorders			
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
ATRIAL FIBRILLATION			

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
CARDIAC ARREST			
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
CARDIAC FAILURE			
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
CARDIAC FAILURE ACUTE			
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
CARDIO-RESPIRATORY ARREST			
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
CARDIOGENIC SHOCK			
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
CARDIOVASCULAR INSUFFICIENCY			
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
MYOCARDIAL INFARCTION			
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
SUPRAVENTRICULAR TACHYCARDIA			

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
VENTRICULAR FIBRILLATION			
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
VENTRICULAR TACHYCARDIA			
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
Nervous system disorders			
CEREBRAL 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 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
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
DEPRESSED LEVEL OF CONSCIOUSNESS			
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
HAEMORRHAGE INTRACRANIAL			
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
ISCHAEMIC STROKE			
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
METABOLIC ENCEPHALOPATHY			

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
NEUROMYOPATHY			
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
SEDATION			
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
SUBARACHNOID 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
Blood and lymphatic system disorders			
ANAEMIA			
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
DISSEMINATED INTRAVASCULAR COAGULATION			
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
THROMBOCYTOPENIA			
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
Ear and labyrinth disorders			
DEAFNESS UNILATERAL			
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
GASTRIC ULCER 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
GASTROINTESTINAL HAEMORRHAGE			
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
ILEUS			
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
INCARCERATED INGUINAL HERNIA			
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
INTESTINAL INFARCTION			
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
INTESTINAL ISCHAEMIA			
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
INTESTINAL 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 / 0	0 / 0	0 / 0
INTESTINAL PERFORATION			

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
INTRA-ABDOMINAL HAEMORRHAGE			
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
ISCHAEMIC ENTERITIS			
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
LARGE 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
LARGE INTESTINE 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
MESENTERIC VEIN THROMBOSIS			
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
RECTAL 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 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
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
Hepatobiliary disorders			
CHOLESTASIS			

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
GALLBLADDER PERFORATION			
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
HEPATIC FAILURE			
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
HEPATIC HAEMATOMA			
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
HEPATORENAL SYNDROME			
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
Skin and subcutaneous tissue disorders			
SKIN NECROSIS			
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
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
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
RENAL FAILURE			
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
Musculoskeletal and connective tissue			

disorders			
FASCIITIS			
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
Infections and infestations			
Nosocomial infection			
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
Sepsis			
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
Septic with 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 / 1
ABDOMINAL ABSCESS			
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
ABDOMINAL SEPSIS			
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
ABSCESS INTESTINAL			
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
BRONCHOPULMONARY ASPERGILLOSIS			
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

CANDIDA INFECTION			
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
CHOLECYSTITIS INFECTIVE			
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
CLOSTRIDIUM DIFFICILE INFECTION			
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
GASTROENTERITIS			
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
IATROGENIC INFECTION			
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
INFECTIOUS PLEURAL EFFUSION			
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
LOWER RESPIRATORY TRACT INFECTION			
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
LUNG ABSCESS			
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
NECROTISING FASCIITIS			

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
NECROTISING SOFT TISSUE INFECTION			
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
PERITONEAL ABSCESS			
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
PERITONITIS			
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
PHARYNGEAL ABSCESS			
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
PNEUMONIA			
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
PNEUMONIA HERPES VIRAL			
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
POSTOPERATIVE WOUND INFECTION			
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
SEPTIC SHOCK			

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
SOFT TISSUE INFECTION			
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
Metabolism and nutrition disorders			
Failure to thrive			
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
CACHEXIA			
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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 112 (50.00%)		
number of deaths (all causes)	33		
number of deaths resulting from adverse events	0		
Vascular disorders			
Shock			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
ARTERIAL HAEMORRHAGE			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ARTERIAL INSUFFICIENCY			
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		
Respiratory, thoracic and mediastinal disorders			
Progressive respiratory insufficiency			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumococcen meningitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ACUTE LUNG INJURY			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
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			
ACUTE MYOCARDIAL INFARCTION				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
CONFUSIONAL STATE				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
ELECTROCARDIOGRAM QT PROLONGED				
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 CONDITION ABNORMAL				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
ABDOMINAL WOUND DEHISCENCE				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ANASTOMOTIC LEAK				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTESTINAL ANASTOMOSIS COMPLICATION				

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

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

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

subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUBARACHNOID HAEMORRHAGE				
subjects affected / exposed	0 / 112 (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	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
DISSEMINATED INTRAVASCULAR COAGULATION				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
THROMBOCYTOPENIA				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
DEAFNESS UNILATERAL				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Intestinal haemorrhage				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bowel obstruction				
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			
ILEUS				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INCARCERATED INGUINAL HERNIA				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTESTINAL INFARCTION				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTESTINAL ISCHAEMIA				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTESTINAL PERFORATION				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTRA-ABDOMINAL HAEMORRHAGE				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ISCHAEMIC ENTERITIS				

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

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

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

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

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

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

Non-serious adverse events	recAP, 0.4 mg/kg	recAP, 0.8 mg/kg	recAP, 1.6 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 38 (92.11%)	31 / 35 (88.57%)	103 / 109 (94.50%)
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	2 / 109 (1.83%)
occurrences (all)	1	2	2
HYPERTENSION			
subjects affected / exposed	2 / 38 (5.26%)	6 / 35 (17.14%)	14 / 109 (12.84%)
occurrences (all)	2	6	14
HYPOTENSION			
subjects affected / exposed	5 / 38 (13.16%)	2 / 35 (5.71%)	6 / 109 (5.50%)
occurrences (all)	5	2	6
PHLEBITIS			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	2 / 109 (1.83%)
occurrences (all)	1	2	2
General disorders and administration site conditions			
GENERALISED OEDEMA			
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	5 / 38 (13.16%)	1 / 35 (2.86%)	10 / 109 (9.17%)
occurrences (all)	5	1	10
TACHYPNOEA			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 109 (0.00%)
occurrences (all)	2	0	0
WHEEZING			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	0 / 109 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
AGITATION			
subjects affected / exposed	2 / 38 (5.26%)	2 / 35 (5.71%)	13 / 109 (11.93%)
occurrences (all)	2	2	13
ANXIETY			
subjects affected / exposed	3 / 38 (7.89%)	2 / 35 (5.71%)	3 / 109 (2.75%)
occurrences (all)	3	2	3
CONFUSIONAL STATE			
subjects affected / exposed	3 / 38 (7.89%)	3 / 35 (8.57%)	7 / 109 (6.42%)
occurrences (all)	3	3	7
DELIRIUM			
subjects affected / exposed	5 / 38 (13.16%)	5 / 35 (14.29%)	14 / 109 (12.84%)
occurrences (all)	5	5	14
DISORIENTATION			
subjects affected / exposed	3 / 38 (7.89%)	1 / 35 (2.86%)	2 / 109 (1.83%)
occurrences (all)	3	1	2
INSOMNIA			
subjects affected / exposed	2 / 38 (5.26%)	2 / 35 (5.71%)	13 / 109 (11.93%)
occurrences (all)	2	2	13
Investigations			
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	3 / 109 (2.75%)
occurrences (all)	2	1	3
BLOOD POTASSIUM DECREASED			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	2 / 109 (1.83%)
occurrences (all)	0	2	2
BREATH SOUNDS ABNORMAL			

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

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

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

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

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

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

subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
INTENSIVE CARE UNIT ACQUIRED WEAKNESS			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	15 / 112 (13.39%)		
occurrences (all)	15		
THROMBOCYTOPENIA			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	6		
THROMBOCYTOSIS			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	9 / 112 (8.04%)		
occurrences (all)	9		
CONSTIPATION			
subjects affected / exposed	13 / 112 (11.61%)		
occurrences (all)	13		
DIARRHOEA			
subjects affected / exposed	12 / 112 (10.71%)		
occurrences (all)	12		
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
ILEUS PARALYTIC			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	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		
FUNGAL INFECTION			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
HERPES SIMPLEX			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
ORAL HERPES			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
PNEUMONIA			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	11		
SEPTIC SHOCK			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	11		
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
HYPERKALAEMIA			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
HYPERNATRAEMIA			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	10		
HYPOALBUMINAEMIA			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
HYPOKALAEMIA			
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		
HYPOPHOSPHATAEMIA			
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	The following is a summary of the major changes implemented with Protocol Amendment 1 version 2.0: • The IND number was added to the protocol. • Study design section was amended in regard to inclusion and exclusion criteria. • 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. • 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. • 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. • 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.
03 February 2016	The following is a summary of the major changes implemented with Protocol Amendment 2 version 3.0: • Addition of new countries and sites and inclusion of text on analysis of patients during interim analysis period. • Study design section had been amended with regard to inclusion and exclusion criteria and end of study was defined as Day 28. • Pharmacokinetic assessments were amended to reflect the subset of patients in whom they were performed. • Recording of concomitant medication use in the electronic case report form (eCRF) was amended to introduce use of mean dosing by the system. • Addition of height for calculation of the body mass index (BMI). • Clarification in weight for calculation of study drug dose and treatment administered. • Addition of a new analysis set (ITT Part 1 Interim Set). Addition of other analysis sets to reflect the current statistical analysis plan (SAP). • Change in cut-off date for capture of unrelated AEs and SAEs. • Update to data to be reviewed by DMC. • Address was updated for PPD Medical Monitor in European Union. • References to para-aminohippuric acid were deleted as it was commercially not available anymore.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported