Clinical trial results:
A RANDOMIZED, DOUBLE BLIND, PLACEBO–CONTROLLED, PHASE 3 STUDY TO ASSESS THE SAFETY AND EFFICACY OF ART-123 IN SUBJECTS WITH SEVERE SEPSIS AND COAGULOPATHY

Summary

EudraCT number	2012-002251-42
Trial protocol	BE NL HU FI CZ ES BG GB DE GR
Global end of trial date	28 February 2019

Results information

Result version number	v1 (current)
This version publication date	12 April 2020
First version publication date	12 April 2020

Trial information

Trial identification

Sponsor protocol code	3-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01598831
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Asahi Kasei Pharma America Corporation
Sponsor organisation address	200 5th Avenue, Waltham, United States,
Public contact	David Fineberg, MD Medical Monitor, Asahi Kasei Pharma America Corporation, 1 7815307191, dfineberg@akpamerica.com
Scientific contact	David Fineberg, MD Medical Monitor, Asahi Kasei Pharma America Corporation, 1 7815307191, dfineberg@akpamerica.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2019
Global end of trial reached?	Yes
Global end of trial date	28 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate whether ART-123, when administered to subjects with bacterial infection complicated by at least one organ dysfunction (septic shock and/or respiratory failure) and coagulopathy, can reduce mortality.

2. To evaluate the safety of ART-123 in this patient population.

Protection of trial subjects:

Critically ill subjects treated and monitored in an ICU or acute care setting. Safety assessments for adverse events, ECGs and laboratory tests were conducted to ensure subject safety.

Background therapy:

In addition to the IMP treatment per study protocol, subjects were treated for sepsis according to the standard of care of the institution.

Evidence for comparator:

No comparators used.

Actual start date of recruitment	29 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 49
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 68
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Finland: 37
Country: Number of subjects enrolled	France: 149
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Brazil: 19

Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	India: 85
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Peru: 5
Country: Number of subjects enrolled	Russian Federation: 111
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United States: 71
Worldwide total number of subjects	800
EEA total number of subjects	376

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)	462
From 65 to 84 years	305
85 years and over	33

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 319 sites in 27 countries; of these, 159 study sites (in 26 countries) assigned participants to study drug treatment. First participant was randomized on Oct 29, 2012 and the last participant was randomized on Mar 8, 2018. Last participant completed long term follow-up (survival only) on Feb 28, 2019.

Pre-assignment

Screening details:

Of 946 consented participants, 816 were randomized to study treatment and 800 received at least one dose of study treatment, 571 completed of 6 consecutive dose. Primary endpoint was assessed at Day 28.

Pre-assignment period milestones

Number of subjects started	816[1]
Number of subjects completed	800

Pre-assignment subject non-completion reasons

Reason: Number of subjects	did not receive a dose of drug: 16

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 816 subjects were enrolled (i.e. randomized) into the 3-001 study but 16 of these subjects did not receive a dose of IMP.

Period 1

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

Blinding implementation details:

Subjects were randomly assigned in a 1:1 ratio to receive either ART-123 or placebo. A vendor, Almac Clinical Services provided an automatic system that generated a unique randomization number to the site at the baseline visit and for an assigned IMP kit number. The study site and Sponsor were blinded. Lab samples were coded and kept blinded. A DMC was unblinded for monitoring safety and only CRO personnel for unblinding safety reports or for follow-up of antibody positive tests were unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	ART-123

Arm description:

Received at least one dose of study drug: ART-123 (thrombomodulin alfa) dosage administered intravenously 0.06 mg/kg/day (up to a maximum dose of 6 mg/day) for 6 consecutive days.

Arm type	Experimental
Investigational medicinal product name	ART-123
Investigational medicinal product code	ART-123
Other name	thrombomodulin alfa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

ART-123 was are administered at the equivalent dose of 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day for six consecutive days. ART-123 is given by intravenous bolus or rapid IV infusion, in which case 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day is diluted in 50 mL of NS and given over a period of 15 minutes.

ART-123 is supplied as individual glass ampules containing 6.0 mg of formulated drug in 1 mL of total volume; with an overfill of 0.1mL. The total volume of each ampule equals 1.1 mL. Stable for up to 18 months when stored at 2°C–8°C. Photostability studies indicate that ART-123 is sensitive to light. The investigational drug product is kept in closed cartons and should be protected from sunlight at all times.

Arm title	Placebo

Arm description:

Subject received at least one dose of study treatment : Placebo was administered intravenously at the equivalent dose of 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day for six consecutive days.

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

Dosage and administration details:

Placebo was administered at the equivalent dose of 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day for six days. Placebo was given by intravenous bolus or rapid IV infusion, in which case 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day is diluted in 50mL of NS and given over a period of 15 minutes.

Placebo for this study was supplied as identically labeled, individual glass ampules in 1 mL of total volume; with an overfill of 0.1mL. The total volume of each ampule equals 1.1 mL. Placebo was maintained refrigerated at 2°C–8°C and protected from light during storage.

Number of subjects in period 1	ART-123	Placebo
Started	395	405
Completed	283	278
Not completed	112	127
Adverse event, serious fatal	104	117
Consent withdrawn by subject	1	1
PI decision	1	-
Various reasons	6	-
varying reasons	-	9

Baseline characteristics

Reporting groups	
Reporting group title	ART-123
Reporting group description:	
Received at least one dose of study drug: ART-123 (thrombomodulin alfa) dosage administered intravenously 0.06 mg/kg/day (up to a maximum dose of 6 mg/day) for 6 consecutive days.	
Reporting group title	Placebo
Reporting group description:	
Subject received at least one dose of study treatment : Placebo was administered intravenously at the equivalent dose of 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day for six consecutive days.	

Reporting group values	ART-123	Placebo	Total
Number of subjects	395	405	800
Age categorical			
Baseline Analysis Population, Full Analysis Set - all randomized and dosed subjects.			
Units: Subjects			
Adults (18-64 years)	231	231	462
From 65-84 years	146	159	305
85 years and over	18	15	33
Gender categorical			
Baseline Analysis Population, Full Analysis Set - All randomized and dosed subjects.			
Units: Subjects			
Female	179	184	363
Male	216	221	437

End points

End points reporting groups

Reporting group title	ART-123
Reporting group description:	
Received at least one dose of study drug: ART-123 (thrombomodulin alfa) dosage administered intravenously 0.06 mg/kg/day (up to a maximum dose of 6 mg/day) for 6 consecutive days.	
Reporting group title	Placebo
Reporting group description:	
Subject received at least one dose of study treatment : Placebo was administered intravenously at the equivalent dose of 0.06 mg/kg/day up to a maximum dose of 6.0 mg/day for six consecutive days.	

Primary: 28-Day All-cause Mortality

End point title	28-Day All-cause Mortality
End point description:	
Mortality status 28 days was determined by evaluating the date of death if a subject died, or the last known contact date if the subject was not known to have died. If the date of death was 28 days or less from the start of treatment the subject was classified as dead at 28 days after the start of treatment (Mortality Day 28).	
End point type	Primary
End point timeframe:	
Through Day 28	

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	405		
Units: Participants	106	119		

Statistical analyses

Statistical analysis title	28-Day All-cause Mortality Analysis
Comparison groups	ART-123 v Placebo
Number of subjects included in analysis	800
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.318 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.68
upper limit	8.77

Notes:

[1] - p-value is calculated value, not the a priori threshold for statistical significance. The threshold for statistical significance was a two sided 5%.

Estimation Comment: Rates by Arm are 26.8% for ART-123 and 29.4% for Placebo

Primary: On-Treatment Serious Major Bleeding Events – Primary Safety outcome measure

End point title	On-Treatment Serious Major Bleeding Events – Primary Safety outcome measure[2]

End point description:

On-treatment Serious Major Bleeding Events collected as Serious Adverse Events and defined as: any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious (e.g., resulting in permanent morbidity), or any bleeding that required the administration of 1440 ml (typically 6 units) of packed red cells over two consecutive days. (Investigator assessment for seriousness criteria.)

End point type	Primary

End point timeframe:

Through Day 28

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was only performed on 28-day mortality. All other endpoints only recorded participant counts per arm.

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395[3]	404[4]		
Units: Participants	23	16		

Notes:

[3] - Safety population: all subjects who received at least 1 dose of study drug

[4] - Safety population: all subjects who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Follow up all-cause mortality at 3 months

End point title	Follow up all-cause mortality at 3 months

End point description:

Subject whose status was alive, or unknown was censored at the last available date that subject was known to be alive.

End point type	Secondary

End point timeframe:

3 months

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	405		
Units: Participants	126	136		

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of organ dysfunction as measured through day 28 by shock free and alive days

End point title	Resolution of organ dysfunction as measured through day 28 by shock free and alive days

End point description:

The number of event free and alive days was calculated as Alive Days - Event Days. Shock days was defined as the number of days on concomitant vasopressor medication as collected in the eCRF.

End point type	Secondary

End point timeframe:

Through Day 28

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	405		
Units: Days				
arithmetic mean (standard deviation)	17.6 (± 10.5)	17.6 (± 10.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of organ dysfunction as measured through day 28 by ventilator free and alive days

End point title	Resolution of organ dysfunction as measured through day 28 by ventilator free and alive days

End point description:

The number of event free and alive days was calculated as Alive Days - Event Days. Ventilator days was defined as the number of days on assisted breathing as collected in the eCRF.

End point type	Secondary

End point timeframe:

Through Day 28

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	405		
Units: Days				
arithmetic mean (standard deviation)	15.8 (± 11.75)	14.5 (± 11.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of organ dysfunction as measured through day 28 by dialysis free and alive days

End point title	Resolution of organ dysfunction as measured through day 28 by dialysis free and alive days

End point description:

The number of event free and alive days was calculated as Alive Days - Event Days. Dialysis days was defined as the number of days on dialysis as collected in the eCRF

End point type	Secondary

End point timeframe:

Through Day 28

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	405		
Units: Days				
arithmetic mean (standard deviation)	20.2 (± 11.05)	19.6 (± 11.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of Anti-drug antibodies up to 18 months

End point title	Presence of Anti-drug antibodies up to 18 months

End point description:

Blood samples for analysis of anti-ART-123 antibody were obtained on Day 1 and Day 28 or at early termination. All subjects that developed anti-ART-123 antibodies were followed for blood draw and medical evaluation at 3 month intervals until their serum antibody titer results became negative for a maximum duration of 18 months (ADA Positive Subject Follow-Up).

End point type	Secondary

End point timeframe:

18 Months

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395[5]	404[6]		
Units: Participants	0	0		

Notes:

[5] - Safety population: all subjects who received at least 1 dose of study drug

[6] - Safety population: all subjects who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Post-hoc: Day 28 Mortality in Subjects with INR > 1.4 at Baseline and PLT > 30x10 9th/L at Baseline

End point title	Day 28 Mortality in Subjects with INR > 1.4 at Baseline and PLT > 30x10 9th/L at Baseline

End point description:

Post-hoc analysis of Full Analysis Set. Target subjects: Approximately 80% of patients (634/800) maintained protocol-specified eligibility for coagulopathy (PT-INR >1.40 and PLT >30×109/L before initiating the first dose of study drug (baseline).

End point type	Post-hoc

End point timeframe:

Through Day 28

End point values	ART-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[7]	327[8]		
Units: Participants	82	105		

Notes:

[7] - Subjects with INR > 1.4 at Baseline and PLT > 30K at Baseline

[8] - Subjects with INR > 1.4 at Baseline and PLT > 30K at Baseline

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected between randomization and through Day 28. For SAE, collection started from the time of authorization to randomize the participants.

Adverse event reporting additional description:

AEs were analyzed using a safety population that includes all subjects who received at least 1 dose of study drug. A treatment-emergent adverse event (TEAE) is defined as any AE following exposure to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	ART-123

Reporting group description:

ART-123 (thrombomodulin alfa) dosage administered intravenously 0.06 mg/kg/day (up to a maximum dose of 6 mg/day) for 6 consecutive days. Safety population that includes all subjects who received at least 1 dose of study drug. Any subjects receiving both ART-123 and placebo were included in the ART-123 group.

Reporting group title	Placebo

Reporting group description:

Placebo was administered intravenously at an equivalent dosage of 0.06 mg/kg/day (up to a maximum dose of 6 mg/day) for 6 consecutive days. Safety population that includes all subjects who received at least 1 dose of study drug. Any subjects receiving both ART-123 and placebo were included in the ART-123 group.

Serious adverse events	ART-123	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	206 / 396 (52.02%)	202 / 404 (50.00%)	
number of deaths (all causes)	108	119	
number of deaths resulting from adverse events	7	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	6 / 396 (1.52%)	6 / 404 (1.49%)	
occurrences causally related to treatment / all	1 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	4 / 396 (1.01%)	7 / 404 (1.73%)	
occurrences causally related to treatment / all	0 / 4	2 / 7	
deaths causally related to treatment / all	0 / 3	2 / 6	
Deep vein thrombosis			
subjects affected / exposed	2 / 396 (0.51%)	4 / 404 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	6 / 396 (1.52%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 396 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	2 / 396 (0.51%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic thrombosis			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral coldness			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	24 / 396 (6.06%)	28 / 404 (6.93%)	
occurrences causally related to treatment / all	0 / 24	2 / 28	
deaths causally related to treatment / all	0 / 23	1 / 27	
Death			

subjects affected / exposed	0 / 396 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyrexia			
subjects affected / exposed	2 / 396 (0.51%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haematoma			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organ failure			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Pelvic fluid collection			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	11 / 396 (2.78%)	14 / 404 (3.47%)	
occurrences causally related to treatment / all	1 / 11	0 / 14	
deaths causally related to treatment / all	1 / 5	0 / 5	
Acute respiratory distress syndrome			
subjects affected / exposed	8 / 396 (2.02%)	9 / 404 (2.23%)	
occurrences causally related to treatment / all	1 / 8	1 / 9	
deaths causally related to treatment / all	0 / 4	0 / 3	

Acute respiratory failure			
subjects affected / exposed	5 / 396 (1.26%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pneumothorax			
subjects affected / exposed	1 / 396 (0.25%)	4 / 404 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 396 (0.51%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 396 (0.51%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 396 (0.51%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 396 (0.51%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 396 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute pulmonary oedema			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragm muscle weakness			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haematoma			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory arrest			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract oedema			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 396 (0.51%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma scale abnormal			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glutamate dehydrogenase increased			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio abnormal			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	6 / 396 (1.52%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	4 / 6	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Overdose			

subjects affected / exposed	1 / 396 (0.25%)	4 / 404 (0.99%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic leak			
subjects affected / exposed	1 / 396 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wound dehiscence			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical peritonitis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			

subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	10 / 396 (2.53%)	11 / 404 (2.72%)	
occurrences causally related to treatment / all	1 / 10	0 / 11	
deaths causally related to treatment / all	0 / 3	0 / 5	
Atrial fibrillation			
subjects affected / exposed	6 / 396 (1.52%)	5 / 404 (1.24%)	
occurrences causally related to treatment / all	1 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	4 / 396 (1.01%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure acute			
subjects affected / exposed	4 / 396 (1.01%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Cardiopulmonary failure			
subjects affected / exposed	2 / 396 (0.51%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Myocardial infarction			
subjects affected / exposed	1 / 396 (0.25%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	3 / 396 (0.76%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 396 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	2 / 396 (0.51%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiogenic shock			

subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	4 / 396 (1.01%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 396 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Embolic cerebral infarction			

subjects affected / exposed	2 / 396 (0.51%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epilepsy			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care unit acquired weakness			
subjects affected / exposed	0 / 396 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain injury			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem ischaemia			

subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral atrophy			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnic coma			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	10 / 396 (2.53%)	12 / 404 (2.97%)	
occurrences causally related to treatment / all	2 / 10	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 396 (1.26%)	7 / 404 (1.73%)	
occurrences causally related to treatment / all	1 / 5	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 396 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coagulopathy			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilia			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	7 / 396 (1.77%)	6 / 404 (1.49%)	
occurrences causally related to treatment / all	2 / 7	1 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 396 (0.51%)	5 / 404 (1.24%)	
occurrences causally related to treatment / all	1 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	3 / 396 (0.76%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Intestinal perforation			

subjects affected / exposed	3 / 396 (0.76%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 396 (0.25%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 396 (0.51%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 32	0 / 36	
Fistula of small intestine			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal wall abnormal			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mesenteric haemorrhage			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis mesenteric vessel			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	3 / 396 (0.76%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 396 (0.25%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatocellular injury			
subjects affected / exposed	2 / 396 (0.51%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic necrosis			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	14 / 396 (3.54%)	10 / 404 (2.48%)	
occurrences causally related to treatment / all	2 / 14	3 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	3 / 396 (0.76%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 396 (0.51%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal ischaemia			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			

subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal haemorrhage			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	2 / 396 (0.51%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	28 / 396 (7.07%)	30 / 404 (7.43%)	
occurrences causally related to treatment / all	1 / 28	1 / 30	
deaths causally related to treatment / all	1 / 25	1 / 28	
Sepsis			
subjects affected / exposed	8 / 396 (2.02%)	11 / 404 (2.72%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 7	0 / 10	
Pneumonia			
subjects affected / exposed	8 / 396 (2.02%)	10 / 404 (2.48%)	
occurrences causally related to treatment / all	0 / 8	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 3	

Peritonitis			
subjects affected / exposed	3 / 396 (0.76%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gangrene			
subjects affected / exposed	3 / 396 (0.76%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 396 (0.25%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Endocarditis			
subjects affected / exposed	2 / 396 (0.51%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	1 / 396 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis gangrenous			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex pneumonia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective aneurysm			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia fungal			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic embolus			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster pneumonia			

subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 396 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			

subjects affected / exposed	0 / 396 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ART-123	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	271 / 396 (68.43%)	264 / 404 (65.35%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	23 / 396 (5.81%)	24 / 404 (5.94%)	
occurrences (all)	30	27	
Hypertension			
subjects affected / exposed	23 / 396 (5.81%)	25 / 404 (6.19%)	
occurrences (all)	25	28	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	51 / 396 (12.88%)	52 / 404 (12.87%)	
occurrences (all)	56	60	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	99 / 396 (25.00%)	78 / 404 (19.31%)	
occurrences (all)	150	100	
Thrombocytopenia			
subjects affected / exposed	40 / 396 (10.10%)	51 / 404 (12.62%)	
occurrences (all)	52	62	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	39 / 396 (9.85%)	33 / 404 (8.17%)	
occurrences (all)	50	38	
Oedema peripheral			
subjects affected / exposed	20 / 396 (5.05%)	17 / 404 (4.21%)	
occurrences (all)	21	17	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	37 / 396 (9.34%)	37 / 404 (9.16%)	
occurrences (all)	37	40	
Diarrhoea			
subjects affected / exposed	31 / 396 (7.83%)	36 / 404 (8.91%)	
occurrences (all)	32	36	
Nausea			
subjects affected / exposed	31 / 396 (7.83%)	18 / 404 (4.46%)	
occurrences (all)	34	19	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	27 / 396 (6.82%)	31 / 404 (7.67%)	
occurrences (all)	30	34	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	28 / 396 (7.07%)	13 / 404 (3.22%)	
occurrences (all)	31	13	
Psychiatric disorders			
Delirium			
subjects affected / exposed	31 / 396 (7.83%)	21 / 404 (5.20%)	
occurrences (all)	31	21	
Insomnia			
subjects affected / exposed	20 / 396 (5.05%)	21 / 404 (5.20%)	
occurrences (all)	20	21	
Infections and infestations			
Pneumonia			
subjects affected / exposed	21 / 396 (5.30%)	22 / 404 (5.45%)	
occurrences (all)	22	22	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	83 / 396 (20.96%)	69 / 404 (17.08%)	
occurrences (all)	100	83	
Hypophosphataemia			
subjects affected / exposed	46 / 396 (11.62%)	39 / 404 (9.65%)	
occurrences (all)	50	40	
Hyperglycaemia			

subjects affected / exposed	37 / 396 (9.34%)	34 / 404 (8.42%)	
occurrences (all)	40	36	
Hypoglycaemia			
subjects affected / exposed	25 / 396 (6.31%)	31 / 404 (7.67%)	
occurrences (all)	28	33	
Hyperkalaemia			
subjects affected / exposed	83 / 396 (20.96%)	69 / 404 (17.08%)	
occurrences (all)	30	21	
Hypernatraemia			
subjects affected / exposed	21 / 396 (5.30%)	23 / 404 (5.69%)	
occurrences (all)	25	22	
Hypomagnesaemia			
subjects affected / exposed	25 / 396 (6.31%)	19 / 404 (4.70%)	
occurrences (all)	26	23	
Fluid overload			
subjects affected / exposed	21 / 396 (5.30%)	16 / 404 (3.96%)	
occurrences (all)	21	16	
Hypocalcaemia			
subjects affected / exposed	21 / 396 (5.30%)	11 / 404 (2.72%)	
occurrences (all)	22	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2013	Amendment v2.0 (13Aug2013) was considered substantial due to changes in the inclusion criteria for 1)alternate criteria for platelet count count added for a 30% decrease in platelets in 24 hours to include subjects with early onset thrombocytopenia, 2) time window for developing evidence of infection revised from 24 to 36 hours to allow the development of infection and time to randomization from 12 to 15 hours due to sites not having enough time to gain legally authorized consent and randomize.
05 September 2014	Amendment v3.0 (21July2014) was considered substantial since it revised an exclusion criteria that had previously excluded subjects on renal replacement treatment. AKPA provided results of a phase 1 study indicating end-stage renal disease (ESRD) subjects undergoing hemodialysis supporting the enrollment of RRT subjects in study 3-001 without any dose adjustment to the study drug.
27 November 2015	Amendment v4.0 (23Oct2015) was considered substantial due to changes widening the inclusion criteria timing. The purpose of this change was to provide more time for investigators to enroll subjects before the time window expires. Therefore in Version 4 of the protocol a change was made to allow up to 36 hours after the first qualifying INR to allow the sites to identify and enroll subjects in a timely manner before the time window expires. This will only occur in cases where the first qualifying INR precedes both thrombocytopenia and organ dysfunction. In consultation with clinical experts, the Sponsor has concluded that the change is justified as it is unlikely to result in a meaningful clinical difference in disease progression that would impact outcomes. The Scenario 2 was eliminated because it was difficult for the sites to justify obtaining the informed consent for the sole purpose of obtaining an INR. The deletion of Scenario 2 does not impact the inclusion criteria for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported