



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 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 (\pm 10.5) | 17.6 (\pm 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 > 30x10⁹/L at Baseline

| | |
|-----------------|---|
| End point title | Day 28 Mortality in Subjects with INR > 1.4 at Baseline and PLT > 30x10 ⁹ /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 occurrences (all) | 37 / 396 (9.34%) 37 | 37 / 404 (9.16%) 40 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 31 / 396 (7.83%) 32 | 36 / 404 (8.91%) 36 | |
| Nausea subjects affected / exposed occurrences (all) | 31 / 396 (7.83%) 34 | 18 / 404 (4.46%) 19 | |
| Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all) | 27 / 396 (6.82%) 30 | 31 / 404 (7.67%) 34 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 28 / 396 (7.07%) 31 | 13 / 404 (3.22%) 13 | |
| Psychiatric disorders Delirium subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) | 31 / 396 (7.83%) 31 20 / 396 (5.05%) 20 | 21 / 404 (5.20%) 21 21 / 404 (5.20%) 21 | |
| Infections and infestations Pneumonia subjects affected / exposed occurrences (all) | 21 / 396 (5.30%) 22 | 22 / 404 (5.45%) 22 | |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all) Hyperglycaemia | 83 / 396 (20.96%) 100 46 / 396 (11.62%) 50 | 69 / 404 (17.08%) 83 39 / 404 (9.65%) 40 | |

| | | | |
|-----------------------------|-------------------|-------------------|--|
| 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