



Clinical trial results:

Multicenter, Randomized, Active-Controlled Efficacy And Safety Study Comparing Extended Duration Betrixaban With Standard Of Care Enoxaparin For The Prevention Of Venous Thromboembolism In Acute Medically Ill Patients

Summary

| | |
|--------------------------|---|
| EudraCT number | 2012-000255-13 |
| Trial protocol | BE LV DE ES GB PL LT AT DK CZ BG IT FI SK |
| Global end of trial date | 31 January 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 02 December 2017 |
| First version publication date | 02 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 11-019 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01583218 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Portola Pharmaceuticals, Inc. |
| Sponsor organisation address | 270 East Grand Avenue, South San Francisco, United States, |
| Public contact | Janice Castillo (VP Reg Affairs), Portola Pharmaceuticals, Inc., 001 650-246-7360, jcastillo@portola.com |
| Scientific contact | Janice Castillo (VP Reg Affairs), Portola Pharmaceuticals, Inc., 001 650-246-7360, jcastillo@portola.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 April 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 December 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Demonstrate the superiority of extended duration (35 days + 7 day window, i.e. 35-42 days allowed) anticoagulation with betrixaban as compared to the standard of care (10 ± 4 days) with enoxaparin for prevention of VTE in patients who are at risk due to acute medical illness

Protection of trial subjects:

The conduct of this clinical study met local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 30 March 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Poland: 369 |
| Country: Number of subjects enrolled | Slovakia: 105 |
| Country: Number of subjects enrolled | Spain: 412 |
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Country: Number of subjects enrolled | Austria: 15 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Bulgaria: 431 |
| Country: Number of subjects enrolled | Czech Republic: 237 |
| Country: Number of subjects enrolled | Denmark: 12 |
| Country: Number of subjects enrolled | Estonia: 205 |
| Country: Number of subjects enrolled | Finland: 26 |
| Country: Number of subjects enrolled | France: 292 |
| Country: Number of subjects enrolled | Germany: 196 |
| Country: Number of subjects enrolled | Hungary: 252 |
| Country: Number of subjects enrolled | Italy: 261 |
| Country: Number of subjects enrolled | Latvia: 319 |
| Country: Number of subjects enrolled | Lithuania: 470 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Singapore: 1 |
| Country: Number of subjects enrolled | Belarus: 69 |
| Country: Number of subjects enrolled | Croatia: 92 |
| Country: Number of subjects enrolled | Georgia: 260 |
| Country: Number of subjects enrolled | Romania: 170 |
| Country: Number of subjects enrolled | Russian Federation: 971 |
| Country: Number of subjects enrolled | Serbia: 115 |
| Country: Number of subjects enrolled | Turkey: 54 |
| Country: Number of subjects enrolled | Ukraine: 886 |
| Country: Number of subjects enrolled | Australia: 20 |
| Country: Number of subjects enrolled | Israel: 99 |
| Country: Number of subjects enrolled | South Africa: 91 |
| Country: Number of subjects enrolled | Argentina: 215 |
| Country: Number of subjects enrolled | Brazil: 57 |
| Country: Number of subjects enrolled | Chile: 44 |
| Country: Number of subjects enrolled | Peru: 152 |
| Country: Number of subjects enrolled | Canada: 51 |
| Country: Number of subjects enrolled | United States: 527 |
| Worldwide total number of subjects | 7513 |
| EEA total number of subjects | 3901 |

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) | 782 |
| From 65 to 84 years | 5569 |
| 85 years and over | 1162 |

Subject disposition

Recruitment

Recruitment details:

Patients enrolled with one of the diagnoses: acutely decompensated heart failure, acute respiratory failure, acute infection, rheumatic disease, and ischemic stroke. They also were required to meet additional criteria that placed them at high prolonged risk of VTE. Patients were randomized 1:1 to either betrixaban or enoxaparin treatment group.

Pre-assignment

Screening details:

To maintain the blind, patients assigned to the betrixaban group received betrixaban capsules for 35 to 42 days and daily subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days, and patients assigned to the enoxaparin group received daily SQ injections of enoxaparin for 10 ± 4 days and betrixaban placebo capsules for 35 to 42 days.

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Betrixaban |

Arm description:

Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Betrixaban |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Daily oral (PO) betrixaban capsules for 35 to 42 days

| | |
|------------------|------------|
| Arm title | Enoxaparin |
|------------------|------------|

Arm description:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Enoxaparin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days

| Number of subjects in period 1 | Betrixaban | Enoxaparin |
|--|------------|------------|
| Started | 3759 | 3754 |
| Completed | 3470 | 3471 |
| Not completed | 289 | 283 |
| Adverse event, serious fatal | 206 | 211 |
| Patient was randomized due to mistake | 1 | - |
| Patient deemed ineligible after randomization | 2 | - |
| Subject moved to another province | - | 1 |
| Cannot Contact Patient Directly | 1 | 2 |
| WOC on day of randomization, no IP administered | 1 | - |
| Patient was early terminated from the study | - | 1 |
| Patient randomized but not dosed | 17 | 16 |
| Consent withdrawn by subject | 43 | 29 |
| Adverse event, non-fatal | 3 | 3 |
| Patient did not wish to attend visit at the clinic | - | 1 |
| Patient/Family Decision | 3 | - |
| Source document/coordinator missing | - | 2 |
| Lost to follow-up | 11 | 17 |
| Patient was assessed via phone in person | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Betrixaban |
|-----------------------|------------|

Reporting group description:

Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days

| | |
|-----------------------|------------|
| Reporting group title | Enoxaparin |
|-----------------------|------------|

Reporting group description:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days

| Reporting group values | Betrixaban | Enoxaparin | Total |
|---|------------|------------|-------|
| Number of subjects | 3759 | 3754 | 7513 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 384 | 398 | 782 |
| From 65-84 years | 2767 | 2802 | 5569 |
| 85 years and over | 608 | 554 | 1162 |
| Gender categorical Units: Subjects | | | |
| Female | 2054 | 2034 | 4088 |
| Male | 1705 | 1720 | 3425 |

End points

End points reporting groups

| | |
|--|------------|
| Reporting group title | Betrixaban |
| Reporting group description: Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days | |
| Reporting group title | Enoxaparin |
| Reporting group description: Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days | |

Primary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3

| | |
|---|--|
| End point title | Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3 |
| End point description: Percentage of participants experiencing either symptomatic DVT, non-fatal PE, VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3, or a blinded ultrasound core laboratory measuring of asymptomatic proximal DVT between randomization and Day 47. Visit 3 is between day 35-42 after randomization (day 1). | |
| End point type | Primary |
| End point timeframe: Between randomization and Day 47 (max) | |

| End point values | Betrixaban | Enoxaparin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1914 | 1956 | | |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 6.90 (5.76 to 8.03) | 8.49 (7.25 to 9.72) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Primary: Efficacy Endpoint |
| Statistical analysis description: Cohort 1 (participants with baseline D-dimer $\geq 2 \times$ ULN as determined by the local lab) of the PEOP population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components. | |
| Comparison groups | Betrixaban v Enoxaparin |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 3870 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.054 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction (RRR) |
| Point estimate | 0.194 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.004 |
| upper limit | 0.353 |

Primary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3

| | |
|-----------------|--|
| End point title | Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3 |
|-----------------|--|

End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3, or a blinded ultrasound core laboratory measuring of asymptomatic proximal DVT between randomization and Day 47. Visit 3 is between day 35-42 after randomization (day 1).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Between randomization and Day 47 (max)

| End point values | Betrixaban | Enoxaparin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2842 | 2893 | | |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 5.63 (4.78 to 6.48) | 7.05 (6.12 to 7.98) | | |

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Primary: Efficacy Endpoint |
|----------------------------|----------------------------|

Statistical analysis description:

Cohort 2 (participants with baseline D-dimer $\geq 2 \times$ ULN as determined by the local lab or age ≥ 75 years) of the PEOP population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

| | |
|-------------------|-------------------------|
| Comparison groups | Betrixaban v Enoxaparin |
|-------------------|-------------------------|

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 5735 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.029 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction (RRR) |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.023 |
| upper limit | 0.345 |

Primary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3

| | |
|-----------------|--|
| End point title | Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3 |
|-----------------|--|

End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3, or a blinded ultrasound core laboratory measuring of asymptomatic proximal DVT between randomization and Day 47. Visit 3 is between day 35-42 after randomization (day 1).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Between randomization and Day 47 (max)

| End point values | Betrixaban | Enoxaparin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3112 | 3174 | | |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 5.30 (4.51 to 6.09) | 7.03 (6.14 to 7.91) | | |

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Primary: Efficacy Endpoint |
|----------------------------|----------------------------|

Statistical analysis description:

The PEOP population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

| | |
|-------------------|-------------------------|
| Comparison groups | Betrixaban v Enoxaparin |
|-------------------|-------------------------|

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 6286 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction (RRR) |
| Point estimate | 0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.077 |
| upper limit | 0.375 |

Primary: Percentage of participants experiencing major bleeding through seven days after discontinuation of all study medication

| | |
|--|---|
| End point title | Percentage of participants experiencing major bleeding through seven days after discontinuation of all study medication |
| End point description: Percentage of participants experiencing at least one major bleeding adjudicated by a blinded independent CEC between randomization (day 1) and up to seven days after discontinuation of all study medication. | |
| End point type | Primary |
| End point timeframe: Between randomization and Day 49 (max) | |

| End point values | Betrixaban | Enoxaparin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3716 | 3716 | | |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 0.67 (0.41 to 0.94) | 0.57 (0.32 to 0.81) | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Primary: Safety Analysis |
| Statistical analysis description: Safety population which consisted of all participants who had taken at least one dose of study drug. | |
| Comparison groups | Betrixaban v Enoxaparin |

| | |
|---|---------------|
| Number of subjects included in analysis | 7432 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.554 |
| Method | Chi-squared |

Secondary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3

| | |
|-----------------|---|
| End point title | Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3 |
|-----------------|---|

End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, or VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3. Visit 3 is between day 35-42 after randomization (day 1).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Between randomization and Day 42 (max)

| End point values | Betrixaban | Enoxaparin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2314 | 2313 | | |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 1.30 (0.84 to 1.76) | 1.90 (1.35 to 2.46) | | |

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Secondary: Efficacy Analysis |
|----------------------------|------------------------------|

Statistical analysis description:

Cohort 1 (participants with baseline D-dimer $\geq 2 \times$ ULN as determined by the local lab) of the mITT population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

| | |
|---|-------------------------------|
| Comparison groups | Betrixaban v Enoxaparin |
| Number of subjects included in analysis | 4627 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.092 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction (RRR) |
| Point estimate | 0.326 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.069 |
| upper limit | 0.576 |

Secondary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3

| | |
|-----------------|---|
| End point title | Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3 |
|-----------------|---|

End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, or VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3. Visit 3 is between day 35-42 after randomization (day 1).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Between randomization and Day 42 (max)

| End point values | Betrixaban | Enoxaparin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3407 | 3391 | | |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 1.03 (0.69 to 1.37) | 1.45 (1.04 to 1.85) | | |

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Secondary: Efficacy Analysis |
|----------------------------|------------------------------|

Statistical analysis description:

Cohort 2 (participants with baseline D-dimer $\geq 2 \times$ ULN as determined by the local lab or age ≥ 75 years) of the mITT population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

| | |
|---|-------------------------------|
| Comparison groups | Betrixaban v Enoxaparin |
| Number of subjects included in analysis | 6798 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.11 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction (RRR) |
| Point estimate | 0.295 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.085 |
| upper limit | 0.542 |

Secondary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3

| | |
|-----------------|---|
| End point title | Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3 |
|-----------------|---|

End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, or VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3. Visit 3 is between day 35-42 after randomization (day 1).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Between randomization and Day 42 (max)

| End point values | Betrixaban | Enoxaparin | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3721 | 3720 | | |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 0.94 (0.63 to 1.25) | 1.45 (1.07 to 1.84) | | |

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Secondary: Efficacy Analysis |
|----------------------------|------------------------------|

Statistical analysis description:

The mITT population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

| | |
|---|-------------------------------|
| Comparison groups | Betrixaban v Enoxaparin |
| Number of subjects included in analysis | 7441 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.039 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction (RRR) |
| Point estimate | 0.358 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 0.58 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose date (including) till the end of study

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Betrixaban |
|-----------------------|------------|

Reporting group description:

Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days

| | |
|-----------------------|------------|
| Reporting group title | Enoxaparin |
|-----------------------|------------|

Reporting group description:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days

| Serious adverse events | Betrixaban | Enoxaparin | |
|---|------------------------|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 657 / 3716 (17.68%) | 615 / 3716 (16.55%) | |
| number of deaths (all causes) | 213 | 214 | |
| number of deaths resulting from adverse events | 206 | 211 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 10 / 3716 (0.27%) | 8 / 3716 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 4 | |
| Cervix carcinoma | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cancer | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Rectal cancer | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Brain neoplasm | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bronchial carcinoma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Colorectal cancer | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal stromal tumour | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung carcinoma cell type unspecified stage IV | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant pleural effusion | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastasis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm malignant | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Hodgkin's lymphoma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasmacytoma | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural mesothelioma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectosigmoid cancer | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Throat cancer | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval cancer | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 16 / 3716 (0.43%) | 38 / 3716 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 38 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 8 / 3716 (0.22%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haematoma | | | |
| subjects affected / exposed | 5 / 3716 (0.13%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic vasculitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aneurysm | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angiopathy | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Arterial disorder | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial stenosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism arterial | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Essential hypertension | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral artery aneurysm | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal haematoma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis superficial | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| 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 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Coronary artery bypass | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glaucoma surgery | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hospitalisation | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hysterectomy | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leg amputation | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve repair | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgery | | | |

| | | | |
|--|------------------|-------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 9 / 3716 (0.24%) | 16 / 3716 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 9 | 0 / 16 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 6 / 3716 (0.16%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 5 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 6 / 3716 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 6 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 6 / 3716 (0.16%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 1 | |
| Sudden death | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 3 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac death | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Condition aggravated | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Discomfort | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibrosis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Puncture site haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcer | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| Activities of daily living impaired | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervix haemorrhage uterine | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-------------------|-------------------|--|
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 38 / 3716 (1.02%) | 43 / 3716 (1.16%) | |
| occurrences causally related to treatment / all | 0 / 41 | 0 / 47 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 6 | |
| Respiratory failure | | | |
| subjects affected / exposed | 30 / 3716 (0.81%) | 17 / 3716 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 32 | 1 / 17 | |
| deaths causally related to treatment / all | 0 / 13 | 1 / 7 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 11 / 3716 (0.30%) | 26 / 3716 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 26 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 10 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 13 / 3716 (0.35%) | 9 / 3716 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 11 | 0 / 4 | |
| Epistaxis | | | |
| subjects affected / exposed | 10 / 3716 (0.27%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 10 / 10 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 6 / 3716 (0.16%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |

| | | | |
|---|------------------|------------------|--|
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 3716 (0.16%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alveolitis allergic | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chylothorax | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Emphysema | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paranasal cyst | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major depression | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspiration bronchial | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatine increased | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood urea increased | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood urine present | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheterisation cardiac | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (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 | | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Accident | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Latrogenic injury | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax traumatic | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin injury | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord injury | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic fracture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic haematoma | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (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 failure | | | |
| subjects affected / exposed | 83 / 3716 (2.23%) | 66 / 3716 (1.78%) | |
| occurrences causally related to treatment / all | 0 / 85 | 0 / 70 | |
| deaths causally related to treatment / all | 0 / 30 | 0 / 33 | |
| Atrial fibrillation | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 11 / 3716 (0.30%) | 23 / 3716 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 23 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 10 / 3716 (0.27%) | 15 / 3716 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 10 / 3716 (0.27%) | 12 / 3716 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 8 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 13 / 3716 (0.35%) | 9 / 3716 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 2 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 6 / 3716 (0.16%) | 12 / 3716 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 7 / 3716 (0.19%) | 10 / 3716 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 5 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 9 / 3716 (0.24%) | 6 / 3716 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 5 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 7 / 3716 (0.19%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 5 | |
| Coronary artery disease | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 8 / 3716 (0.22%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 7 / 3716 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 6 / 3716 (0.16%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 5 / 3716 (0.13%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 6 / 3716 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 5 / 3716 (0.13%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Ventricular tachycardia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 3716 (0.11%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiovascular disorder | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cor pulmonale | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sick sinus syndrome | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sinoatrial block | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress cardiomyopathy | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trifascicular block | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular hypokinesia | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| 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 | 19 / 3716 (0.51%) | 35 / 3716 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 19 | 0 / 35 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 12 | |
| Brain oedema | | | |
| subjects affected / exposed | 8 / 3716 (0.22%) | 10 / 3716 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 9 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 7 / 3716 (0.19%) | 6 / 3716 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | |
| Syncope | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 3716 (0.11%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 4 / 3716 (0.11%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic transformation stroke | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral ischaemia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraventricular haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neuroglycopenia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological decompensation | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paralysis flaccid | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Unresponsive to stimuli | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 3716 (0.22%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 2 / 8 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coagulopathy | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polycythaemia | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spontaneous haematoma | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 18 / 3716 (0.48%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 14 / 18 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 15 / 3716 (0.40%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 11 / 15 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|------------------|------------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngo-oesophageal diverticulum | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal strangulated hernia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| 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 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer perforation | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroduodenal haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal polyp haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Volvulus | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 4 / 3716 (0.11%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stone | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic hepatitis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute generalised exanthematous pustulosis | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pemphigoid | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Petechiae | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 10 / 3716 (0.27%) | 15 / 3716 (0.40%) | |
| occurrences causally related to treatment / all | 2 / 10 | 1 / 15 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Renal failure acute | | | |
| subjects affected / exposed | 12 / 3716 (0.32%) | 11 / 3716 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haematuria | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 17 / 3716 (0.46%) | 5 / 3716 (0.13%) | |
| occurrences causally related to treatment / all | 11 / 17 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure chronic | | | |
| subjects affected / exposed | 8 / 3716 (0.22%) | 4 / 3716 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 9 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glomerulonephritis rapidly progressive | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephropathy | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral haemorrhage | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoparathyroidism | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|------------------|------------------|--|
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chondrocalcinosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coccydynia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polymyositis | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scleroderma | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 46 / 3716 (1.24%) | 64 / 3716 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 49 | 0 / 66 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 15 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 13 / 3716 (0.35%) | 11 / 3716 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 13 / 3716 (0.35%) | 7 / 3716 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 9 | 0 / 2 | |
| Septic shock | | | |
| subjects affected / exposed | 7 / 3716 (0.19%) | 8 / 3716 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 5 | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 3716 (0.08%) | 7 / 3716 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 6 / 3716 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 4 / 3716 (0.11%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 4 / 3716 (0.11%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 4 / 3716 (0.11%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium colitis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal bacterial infection | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| 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 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mastoiditis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nosocomial infection | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoas abscess | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyelocystitis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| 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 | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary tuberculosis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Abscess bacterial | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone abscess | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridial infection | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis bacterial | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gallbladder empyema | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 3 / 3716 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 2 / 3716 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 3716 (0.05%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| 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 / 3716 (0.03%) | 0 / 3716 (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 / 3716 (0.00%) | 1 / 3716 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 3716 (0.03%) | 0 / 3716 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Betrixaban | Enoxaparin | |
|---|---------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 879 / 3716 (23.65%) | 779 / 3716 (20.96%) | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 29 / 3716 (0.78%) | 58 / 3716 (1.56%) | |
| occurrences (all) | 29 | 59 | |
| Hypertension | | | |
| subjects affected / exposed | 88 / 3716 (2.37%) | 80 / 3716 (2.15%) | |
| occurrences (all) | 95 | 86 | |
| Cardiac disorders | | | |

| | | | |
|--|--------------------|--------------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 50 / 3716 (1.35%) | 85 / 3716 (2.29%) | |
| occurrences (all) | 53 | 89 | |
| Cardiac failure | | | |
| subjects affected / exposed | 48 / 3716 (1.29%) | 32 / 3716 (0.86%) | |
| occurrences (all) | 49 | 33 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 41 / 3716 (1.10%) | 49 / 3716 (1.32%) | |
| occurrences (all) | 41 | 49 | |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 38 / 3716 (1.02%) | 41 / 3716 (1.10%) | |
| occurrences (all) | 38 | 41 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 74 / 3716 (1.99%) | 59 / 3716 (1.59%) | |
| occurrences (all) | 77 | 65 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 44 / 3716 (1.18%) | 29 / 3716 (0.78%) | |
| occurrences (all) | 44 | 35 | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 39 / 3716 (1.05%) | 19 / 3716 (0.51%) | |
| occurrences (all) | 39 | 19 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 109 / 3716 (2.93%) | 102 / 3716 (2.74%) | |
| occurrences (all) | 114 | 102 | |
| Diarrhoea | | | |
| subjects affected / exposed | 63 / 3716 (1.70%) | 59 / 3716 (1.59%) | |
| occurrences (all) | 68 | 61 | |
| Nausea | | | |
| subjects affected / exposed | 67 / 3716 (1.80%) | 55 / 3716 (1.48%) | |
| occurrences (all) | 72 | 57 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---------------------------------------|--------------------|-------------------|--|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 53 / 3716 (1.43%) | 41 / 3716 (1.10%) | |
| occurrences (all) | 55 | 44 | |
| Epistaxis | | | |
| subjects affected / exposed | 48 / 3716 (1.29%) | 19 / 3716 (0.51%) | |
| occurrences (all) | 54 | 19 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 87 / 3716 (2.34%) | 89 / 3716 (2.40%) | |
| occurrences (all) | 90 | 90 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 46 / 3716 (1.24%) | 23 / 3716 (0.62%) | |
| occurrences (all) | 49 | 25 | |
| Renal cyst | | | |
| subjects affected / exposed | 55 / 3716 (1.48%) | 47 / 3716 (1.26%) | |
| occurrences (all) | 55 | 47 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 110 / 3716 (2.96%) | 78 / 3716 (2.10%) | |
| occurrences (all) | 112 | 84 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 91 / 3716 (2.45%) | 84 / 3716 (2.26%) | |
| occurrences (all) | 100 | 90 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 23 April 2012 | <ul style="list-style-type: none">•Modification of Inclusion and Exclusion Criteria.•Addition of Day 4 of study procedures.•Modification of Statistical Considerations.•Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency. |
| 15 February 2013 | <ul style="list-style-type: none">•Modification of Inclusion and Exclusion Criteria.•Addition of a Post Randomization Dose Reductions.•Modification of Statistical Considerations.•Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency. |
| 04 June 2014 | <ul style="list-style-type: none">•Modification of Inclusion and Exclusion Criteria to exclude enrollment of patients in the biomarker negative subgroup (age <75 and D-dimer <2x ULN)•Modification of Statistical Considerations.•Modification to Outcome Adjudication and Definitions to align with modifications to the Clinical Events Committee (CEC) Charter•Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency. |
| 28 January 2016 | <ul style="list-style-type: none">•Update to Statistical Analysis |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported