

**Clinical trial results:**

A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAf) that have undergone a percutaneous coronary intervention (PCI) with stenting (RE-DUAL PCI)

Summary

| | |
|--------------------------|--|
| EudraCT number | 2013-003201-26 |
| Trial protocol | SE DK GR DE PT HU ES FI NL CZ AT IT BE IE SK SI GB BG HR |
| Global end of trial date | 05 June 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 13 December 2021 |
| First version publication date | 21 June 2018 |

Version creation reason

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | 1160.186 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02164864 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | 173 Binger Strasse, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintrriage.rdg@boehringer-ingelheim.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 | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 12 July 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 June 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 June 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare a dual antithrombotic regimen of 110 mg dabigatran etexilate (DE 110) twice daily plus clopidogrel or ticagrelor (110 mg DE-DAT) and 150 mg dabigatran etexilate (DE 150) twice daily plus clopidogrel or ticagrelor (150 mg DE-DAT) with a triple antithrombotic therapy (TAT) of warfarin plus clopidogrel or ticagrelor plus aspirin (warfarin-TAT) in patients with non-valvular atrial fibrillation (NVAf) that underwent a percutaneous coronary intervention (PCI) with stenting.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 06 August 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects**Subjects enrolled per country**

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Argentina: 52 |
| Country: Number of subjects enrolled | Australia: 31 |
| Country: Number of subjects enrolled | Austria: 19 |
| Country: Number of subjects enrolled | Belgium: 47 |
| Country: Number of subjects enrolled | Brazil: 34 |
| Country: Number of subjects enrolled | Bulgaria: 77 |
| Country: Number of subjects enrolled | Canada: 56 |
| Country: Number of subjects enrolled | Chile: 13 |
| Country: Number of subjects enrolled | Colombia: 12 |
| Country: Number of subjects enrolled | Croatia: 41 |
| Country: Number of subjects enrolled | Czechia: 50 |
| Country: Number of subjects enrolled | Denmark: 61 |
| Country: Number of subjects enrolled | Finland: 45 |
| Country: Number of subjects enrolled | France: 102 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Germany: 486 |
| Country: Number of subjects enrolled | Greece: 101 |
| Country: Number of subjects enrolled | Hong Kong: 17 |
| Country: Number of subjects enrolled | Hungary: 119 |
| Country: Number of subjects enrolled | India: 35 |
| Country: Number of subjects enrolled | Ireland: 15 |
| Country: Number of subjects enrolled | Israel: 37 |
| Country: Number of subjects enrolled | Italy: 91 |
| Country: Number of subjects enrolled | Japan: 117 |
| Country: Number of subjects enrolled | Korea, Republic of: 85 |
| Country: Number of subjects enrolled | Mexico: 12 |
| Country: Number of subjects enrolled | Netherlands: 55 |
| Country: Number of subjects enrolled | New Zealand: 5 |
| Country: Number of subjects enrolled | Norway: 62 |
| Country: Number of subjects enrolled | Poland: 99 |
| Country: Number of subjects enrolled | Portugal: 45 |
| Country: Number of subjects enrolled | Russian Federation: 131 |
| Country: Number of subjects enrolled | Singapore: 9 |
| Country: Number of subjects enrolled | Slovakia: 40 |
| Country: Number of subjects enrolled | Slovenia: 16 |
| Country: Number of subjects enrolled | Spain: 121 |
| Country: Number of subjects enrolled | Sweden: 47 |
| Country: Number of subjects enrolled | Taiwan: 37 |
| Country: Number of subjects enrolled | Thailand: 30 |
| Country: Number of subjects enrolled | Turkey: 168 |
| Country: Number of subjects enrolled | United Kingdom: 69 |
| Country: Number of subjects enrolled | United States: 156 |
| Worldwide total number of subjects | 2845 |
| EEA total number of subjects | 1739 |

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) | 652 |
| From 65 to 84 years | 2089 |
| 85 years and over | 104 |

Subject disposition

Recruitment

Recruitment details:

Patients aged ≥ 80 years in the United States of America (USA) were assigned to 110 milligram (mg) Dual antithrombotic therapy with dabigatran etexilate (DE-DAT), 150 mg DE-DAT, or warfarin. All other patients aged ≥ 80 years (for Japan ≥ 70 years) outside of the USA were assigned to 110 mg DE-DAT or warfarin.

Pre-assignment

Screening details:

All patients (Pts) were screened for eligibility to participate in trial. Pts attended specialist sites to ensure that they met all implemented inclusion/exclusion criteria. Pts were not to be randomised to trial drug if any of specific entry criteria was violated. In this study, 2725 Pts were entered & randomised. 2678 Pts were treated.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

A prospective Randomised, open label, blinded endpoint (PROBE) study.

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Dabigatran Etexilate 110mg |

Arm description:

Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.

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

Dosage and administration details:

Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.

| | |
|------------------|----------------------------|
| Arm title | Dabigatran Etexilate 150mg |
|------------------|----------------------------|

Arm description:

Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.

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

Dosage and administration details:

Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.

| | |
|------------------|----------|
| Arm title | Warfarin |
|------------------|----------|

Arm description:

Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Warfarin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible

| Number of subjects in period 1^[1] | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin |
|---|-----------------------------------|-----------------------------------|-----------------|
| Started | 981 | 763 | 981 |
| Completed | 886 | 703 | 849 |
| Not completed | 95 | 60 | 132 |
| Fatal | 55 | 31 | 51 |
| Non-Fatal | 10 | 10 | 8 |
| Consent withdrawn, not due to AE | 21 | 8 | 56 |
| Lost to follow-up | 4 | 3 | 2 |
| Other than stated | 3 | 4 | 14 |
| Protocol deviation | 2 | 4 | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication. No Statistical analysis

Baseline characteristics

Reporting groups

| | |
|---|----------------------------|
| Reporting group title | Dabigatran Etexilate 110mg |
| Reporting group description: | |
| Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months. | |
| Reporting group title | Dabigatran Etexilate 150mg |
| Reporting group description: | |
| Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months. | |
| Reporting group title | Warfarin |
| Reporting group description: | |
| Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible | |

| Reporting group values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin |
|------------------------|----------------------------|----------------------------|----------|
| Number of subjects | 981 | 763 | 981 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|------------|------------|------------|
| Age Continuous | | | |
| Full analysis set (FAS): All consenting patients randomised were analysed in the treatment group to which they were randomised regardless of whether they took trial medication. The start date of the observation period for this analysis set was the date of randomisation. Patients who discontinued trial medication were followed until the end of the trial. Patients who were lost to follow-up for vital status were censored for the primary endpoint at the time of their last known vital status. | | | |
| Units: years | | | |
| arithmetic mean | 71.5 | 68.6 | 71.7 |
| standard deviation | ± 8.87 | ± 7.65 | ± 8.90 |
| Sex: Female, Male | | | |
| Number of subjects is categorized as Male or Female | | | |
| Units: Subjects | | | |
| Female | 253 | 171 | 231 |
| Male | 728 | 592 | 750 |
| Race/Ethnicity, Customized | | | |
| The details on Race has been provided | | | |
| Units: Subjects | | | |
| Asian | 116 | 79 | 125 |
| Black | 5 | 7 | 3 |
| White | 851 | 658 | 835 |
| Other | 5 | 8 | 7 |
| Missing | 4 | 11 | 11 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 70 | 46 | 59 |
| Not Hispanic or Latino | 903 | 700 | 904 |
| Unknown or Not Reported | 8 | 17 | 18 |
| Age, Customized | | | |
| Units: Subjects | | | |

| | | | |
|-------------|-----|-----|-----|
| <80: EU/ROW | 725 | 699 | 718 |
| <80: USA | 54 | 53 | 61 |
| ≥80: EU/ROW | 189 | 3 | 192 |
| ≥80: USA | 13 | 8 | 10 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 2725 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|------|--|--|
| Age Continuous | | | |
| Full analysis set (FAS): All consenting patients randomised were analysed in the treatment group to which they were randomised regardless of whether they took trial medication. The start date of the observation period for this analysis set was the date of randomisation. Patients who discontinued trial medication were followed until the end of the trial. Patients who were lost to follow-up for vital status were censored for the primary endpoint at the time of their last known vital status. | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Number of subjects is categorized as Male or Female | | | |
| Units: Subjects | | | |
| Female | 655 | | |
| Male | 2070 | | |
| Race/Ethnicity, Customized | | | |
| The details on Race has been provided | | | |
| Units: Subjects | | | |
| Asian | 320 | | |
| Black | 15 | | |
| White | 2344 | | |
| Other | 20 | | |
| Missing | 26 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 175 | | |
| Not Hispanic or Latino | 2507 | | |
| Unknown or Not Reported | 43 | | |
| Age, Customized | | | |
| Units: Subjects | | | |
| <80: EU/ROW | 2142 | | |
| <80: USA | 168 | | |
| ≥80: EU/ROW | 384 | | |
| ≥80: USA | 31 | | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Dabigatran Etexilate 110mg |
| Reporting group description: Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months. | |
| Reporting group title | Dabigatran Etexilate 150mg |
| Reporting group description: Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months. | |
| Reporting group title | Warfarin |
| Reporting group description: Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥70 years); 2.0 to 2.5 if feasible | |
| Subject analysis set title | Warfarin (Excluding elder patient outside USA) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients were orally administered warfarin once daily. The warfarin dose was titrated as needed to maintain the target INR of 2.0 to 3.0 ; 2.0 to 2.5 if feasible. Elderly patients who were outside the USA were excluded. | |
| Subject analysis set title | All Dabigatran Etexilate |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients in combined Dabigatran Etexilate group (ie 110 mg DE + 150 mg DE). | |

Primary: Time to first adjudicated ISTH MBE or CRNMBE.

| | |
|--|---|
| End point title | Time to first adjudicated ISTH MBE or CRNMBE. |
| End point description: The patients having event of time to first adjudicated International Society of Thrombosis and Haemostasis (ISTH) Major Bleeding Event (MBE) or Clinically Relevant Non Major Bleeding Event (CRNMBE). | |
| End point type | Primary |
| End point timeframe: up to 30 months | |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[1] | 763 ^[2] | 981 ^[3] | 764 ^[4] |
| Units: participants with event | 151 | 154 | 264 | 196 |

Notes:

[1] - Full Analysis set (FAS) following the intention-to-treat principle.

[2] - Full Analysis set (FAS) following the intention-to-treat principle.

[3] - Full Analysis set (FAS) following the intention-to-treat principle.

[4] - Full Analysis set (FAS) following the intention-to-treat principle.

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

A pre-defined hierarchical testing approach was used. This was the first step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|--------------------------------------|
| Comparison groups | Dabigatran Etxilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| P-value | < 0.0001 ^[6] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 0.63 |

Notes:

[5] - The upper bound of the Wald confidence interval (CI) of the HR of Dabigatran Etxilate 110mg vs Warfarin (one-sided 97.5%) was compared with this noninferiority margin for the testing of non-inferiority. All non-inferiority tests were based on a margin of 1.38.

[6] - A pre-defined hierarchical testing approach was used. P values for noninferiority were calculated at a one-sided alpha level of 0.025

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

A pre-defined hierarchical testing approach was used. This was the second step in hierarchy. Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model. All non-inferiority tests were based on a margin of 1.38.

| | |
|---|--|
| Comparison groups | Dabigatran Etxilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.001 ^[7] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.88 |

Notes:

[7] - P-values for non-inferiority were calculated at a one-sided alpha level of 0.025

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

A pre-defined hierarchical testing approach was used. This was the fourth step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80

or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---------------------------------------|
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[8] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 0.63 |

Notes:

[8] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| A pre-defined hierarchical testing approach was used. This was the sixth step in hierarchy. Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model | |
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[9] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.88 |

Notes:

[9] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to adjudicated Undetermined cause of death

| | |
|---|---|
| End point title | Time to adjudicated Undetermined cause of death |
| End point description: | |
| The patients having event of time to adjudicated Undetermined cause of death. This is referred to a death not attributable to CV death or to a non-CV cause. Inability to classify the cause of death may have been due to lack of information (e.g. the only available information was "patient died") or when there was insufficient supporting information or detail to assign the cause of death. | |
| End point type | Secondary |
| End point timeframe: | |
| up to 30 months | |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[10] | 763 ^[11] | 981 ^[12] | 764 ^[13] |
| Units: participants with event | 4 | 5 | 4 | 3 |

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---------------------------------------|
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9862 ^[14] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.25 |
| upper limit | 3.95 |

Notes:

[14] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---|
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5277 ^[15] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.59 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 6.64 |

Notes:

[15] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to adjudicated Non-CV

| | |
|-----------------|----------------------------|
| End point title | Time to adjudicated Non-CV |
|-----------------|----------------------------|

End point description:

The patients having event of time to adjudicated Non-cardiovascular (Non-CV). Non-CV death was defined as any death with a specific cause that was not thought to be CV. These were possible examples of non-CV causes of death: Pulmonary, Renal, Gastrointestinal, Hepatobiliary, Pancreatic Infection(included sepsis), Inflammatory (e.g. systemic inflammatory response syndrome) or immune (including autoimmune), Haemorrhage that was neither CV bleeding nor a stroke, Non-CV procedure or surgery, Trauma, Suicide, Non-prescription drug reaction or overdose, Prescription drug reaction or overdose, Neurological (non-CV), Malignancy, Other non-CV

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

End point timeframe:

up to 30 months

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[16] | 763 ^[17] | 981 ^[18] | 764 ^[19] |
| Units: participants with event | 14 | 4 | 13 | 8 |

Notes:

[16] - FAS

[17] - FAS

[18] - FAS

[19] - FAS

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---|
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.238 ^[20] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.49 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.15 |
| upper limit | 1.61 |

Notes:

[20] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---------------------------------------|
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8853 ^[21] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 2.25 |

Notes:

[21] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Secondary: Time to adjudicated CV

| | |
|-----------------|------------------------|
| End point title | Time to adjudicated CV |
|-----------------|------------------------|

End point description:

The patients having event of time to adjudicated Cardiovascular (CV) death. CV death included death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedures, death due to CV haemorrhage, and death due to other CV causes.

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

End point timeframe:

up to 30 months

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[22] | 763 ^[23] | 981 ^[24] | 764 ^[25] |
| Units: participants with event | 37 | 21 | 31 | 24 |

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

[25] - FAS

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|--|---------------------------------------|
| Statistical analysis description: | |
| The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model | |
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5252 [26] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.88 |

Notes:

[26] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Statistical analysis description: | |
| Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model | |
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.567 [27] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 1.51 |

Notes:

[27] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to adjudicated all cause death

| | |
|--|-------------------------------------|
| End point title | Time to adjudicated all cause death |
| End point description: The patients having event of time to adjudicated all cause death. All cause death is defined as the death from any cause included CV death, non-CV death, and undetermined cause of death. | |
| End point type | Secondary |
| End point timeframe: up to 30 months | |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[28] | 763 ^[29] | 981 ^[30] | 764 ^[31] |
| Units: participants with event | 55 | 30 | 48 | 35 |

Notes:

[28] - FAS

[29] - FAS

[30] - FAS

[31] - FAS

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model | |
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5579 ^[32] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.65 |

Notes:

[32] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model. | |
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient |

| | |
|---|--------------------------|
| | outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4414 ^[33] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.34 |

Notes:

[33] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated MI

| | |
|------------------------|--|
| End point title | Time to first adjudicated MI |
| End point description: | The patients having event of time to first adjudicated Myocardial Infarction (MI). |
| End point type | Secondary |
| End point timeframe: | up to 30 months |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[34] | 763 ^[35] | 981 ^[36] | 764 ^[37] |
| Units: participants with event | 44 | 26 | 29 | 22 |

Notes:

[34] - FAS

[35] - FAS

[36] - FAS

[37] - FAS

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model |
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.6144 ^[38] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 2.04 |

Notes:

[38] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---------------------------------------|
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0861 ^[39] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 2.41 |

Notes:

[39] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Secondary: Time to first adjudicated Stroke

| | |
|-----------------|----------------------------------|
| End point title | Time to first adjudicated Stroke |
|-----------------|----------------------------------|

End point description:

The patients having event of time to first adjudicated Stroke. Stroke was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction

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

End point timeframe:

up to 30 months

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 | 763 | 981 | 764 |
| Units: participants with event | 17 | 9 | 13 | 8 |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---------------------------------------|
| Statistical analysis description: | |
| The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. | |
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4803 ^[40] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 2.67 |

Notes:

[40] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Statistical analysis description: | |
| Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model | |
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8537 ^[41] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 2.83 |

Notes:

[41] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated SE

| | |
|-----------------|------------------------------|
| End point title | Time to first adjudicated SE |
|-----------------|------------------------------|

End point description:

The patients having event of time to first adjudicated Systemic embolism (SE). SE is an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) and had to be documented by angiography, surgery, scintigraphy, or autopsy.

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

End point timeframe:

up to 30 months

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[42] | 763 ^[43] | 981 ^[44] | 764 ^[45] |
| Units: participants with event | 3 | 1 | 3 | 3 |

Notes:

[42] - FAS

[43] - FAS

[44] - FAS

[45] - FAS

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

| | |
|---|---------------------------------------|
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9388 ^[46] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.19 |
| upper limit | 4.66 |

Notes:

[46] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

| | |
|---|---|
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.303 ^[47] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.03 |
| upper limit | 2.93 |

Notes:

[47] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated ST

| | |
|------------------------|---|
| End point title | Time to first adjudicated ST |
| End point description: | The patients having event of time to first adjudicated Stent Thrombosis (ST). |
| End point type | Secondary |
| End point timeframe: | up to 30 months |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 | 763 | 981 | 764 |
| Units: participants with event | 15 | 7 | 8 | 7 |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model |
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1546 ^[48] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 4.4 |

Notes:

[48] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---|
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9789 ^[49] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 2.81 |

Notes:

[49] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to composite endpoint of death + MI + stroke

| | |
|--|---|
| End point title | Time to composite endpoint of death + MI + stroke |
| End point description: | |
| The patients having event of time to the composite endpoint of death + myocardial infarction (MI) + stroke | |
| End point type | Secondary |
| End point timeframe: | |
| up to 30 months | |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[50] | 763 ^[51] | 981 ^[52] | 764 ^[53] |
| Units: participants with event | 107 | 60 | 80 | 57 |

Notes:

[50] - FAS

[51] - FAS

[52] - FAS

[53] - FAS

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

| | |
|---|---------------------------------------|
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0484 ^[54] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.79 |

Notes:

[54] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---|
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8903 ^[55] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.47 |

Notes:

[55] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to composite event of death or first thrombotic event

| | |
|---|--|
| End point title | Time to composite event of death or first thrombotic event |
| End point description: | |
| The patients having event of time to death or first thrombotic event (all death, myocardial infarction (MI), stroke/systemic embolism (SE)) | |
| End point type | Secondary |
| End point timeframe: | |
| up to 30 months | |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[56] | 763 ^[57] | 981 ^[58] | 764 ^[59] |
| Units: participants with event | 108 | 60 | 83 | 60 |

Notes:

[56] - FAS

[57] - FAS

[58] - FAS

[59] - FAS

| End point values | All Dabigatran Etexilate | | | |
|--------------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1744 ^[60] | | | |
| Units: participants with event | 168 | | | |

Notes:

[60] - FAS

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| A pre-defined hierarchical testing approach was used. This was the fifth step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. | |
| Comparison groups | Warfarin v All Dabigatran Etexilate |

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 2725 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[61] |
| P-value | = 0.1128 ^[62] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.53 |

Notes:

[61] - The upper bound of the Wald confidence interval (CI) of the HR of All Dabigatran EteXilate (110mg and 150 mg) vs Warfarin (one-sided 97.5%) was compared with this noninferiority margin for the testing of non-inferiority. All non-inferiority tests were based on a margin of 1.38.

[62] - P values for noninferiority were calculated at a one-sided alpha level of 0.025

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

| | |
|---|---------------------------------------|
| Comparison groups | Dabigatran EteXilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.072 ^[63] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.73 |

Notes:

[63] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

| | |
|---|---|
| Comparison groups | Dabigatran EteXilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.875 ^[64] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.39 |

Notes:

[64] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated unplanned revascularisation by PCI/CABG

| | |
|---|---|
| End point title | Time to first adjudicated unplanned revascularisation by PCI/CABG |
| End point description: The patients having event of time to first event for adjudicated unplanned revascularisation by Percutaneous Coronary Intervention/Coronary Artery Bypass Graft | |
| End point type | Secondary |
| End point timeframe: up to 30 months | |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[65] | 763 ^[66] | 981 ^[67] | 764 ^[68] |
| Units: participants with event | 76 | 51 | 69 | 52 |

Notes:

[65] - FAS

[66] - FAS

[67] - FAS

[68] - FAS

Statistical analyses

| | |
|--|---------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model | |
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.608 ^[69] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.51 |

Notes:

[69] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model. | |
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8348 ^[70] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.41 |

Notes:

[70] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to death or first thrombotic event or unplanned revascularisation by PCI/CABG

| | |
|---|--|
| End point title | Time to death or first thrombotic event or unplanned revascularisation by PCI/CABG |
| End point description: The patients having event of time to death or first thrombotic event (all death, myocardial infarction, stroke/systemic embolism) or unplanned revascularisation by Percutaneous Coronary Intervention/Coronary Artery Bypass Graft | |
| End point type | Secondary |
| End point timeframe: up to 30 months | |

| End point values | Dabigatran Etexilate 110mg | Dabigatran Etexilate 150mg | Warfarin | Warfarin (Excluding elder patient outside USA) |
|--------------------------------|----------------------------|----------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 981 ^[71] | 763 ^[72] | 981 ^[73] | 764 ^[74] |
| Units: participants with event | 149 | 90 | 131 | 98 |

Notes:

[71] - FAS

[72] - FAS

[73] - FAS

[74] - FAS

| | | | | |
|--------------------------------|--------------------------|--|--|--|
| End point values | All Dabigatran Etexilate | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1744 ^[75] | | | |
| Units: participants with event | 239 | | | |

Notes:

[75] - FAS

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

A pre-defined hierarchical testing approach was used. This was the third step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere].

| | |
|---|-------------------------------------|
| Comparison groups | Warfarin v All Dabigatran Etexilate |
| Number of subjects included in analysis | 2725 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[76] |
| P-value | = 0.0047 ^[77] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.29 |

Notes:

[76] - The upper bound of the Wald confidence interval (CI) of the HR of All Dabigatran Etexilate (110mg and 150 mg) vs Warfarin (one-sided 97.5%) was compared with this noninferiority margin for the testing of non-inferiority. All non-inferiority tests were based on a margin of 1.38.

[77] - P values for noninferiority were calculated at a one-sided alpha level of 0.025

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

| | |
|---|---|
| Comparison groups | Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA) |
| Number of subjects included in analysis | 1527 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4432 ^[78] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.19 |

Notes:

[78] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

| | |
|--|---------------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model | |
| Comparison groups | Dabigatran Etexilate 110mg v Warfarin |
| Number of subjects included in analysis | 1962 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3002 [79] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.43 |

Notes:

[79] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 6 days after the last drug administration.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Dabigatran Etexilate 110mg |
|-----------------------|----------------------------|

Reporting group description:

Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.

| | |
|-----------------------|----------|
| Reporting group title | Warfarin |
|-----------------------|----------|

Reporting group description:

Patients were orally administered one tablet of warfarin 1 mg, 3 mg, or 5 mg once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible

| | |
|-----------------------|----------------------------|
| Reporting group title | Dabigatran Etexilate 150mg |
|-----------------------|----------------------------|

Reporting group description:

Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.

| Serious adverse events | Dabigatran Etexilate 110mg | Warfarin | Dabigatran Etexilate 150mg |
|---|----------------------------|--------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 415 / 972 (42.70%) | 396 / 948 (41.77%) | 300 / 758 (39.58%) |
| number of deaths (all causes) | 38 | 41 | 24 |
| number of deaths resulting from adverse events | 38 | 41 | 24 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acoustic neuroma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 5 / 972 (0.51%) | 4 / 948 (0.42%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign gastrointestinal neoplasm | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer recurrent | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder neoplasm | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone neoplasm | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carcinoma in situ of penis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemangioma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon neoplasm | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colorectal adenocarcinoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma stage IV | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lung carcinoma cell type unspecified stage I | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphocytic leukaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mantle cell lymphoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningioma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to liver | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to spine | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelofibrosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Non-small cell lung cancer recurrent | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Plasma cell myeloma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 6 / 972 (0.62%) | 3 / 948 (0.32%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer stage 0 | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin cancer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the tongue | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Testicular neoplasm | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma recurrent | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour ulceration | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary bladder adenoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aneurysm | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angiodysplasia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic dissection rupture | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Aortic necrosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic stenosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 972 (0.31%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic thrombosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortitis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic vascular disorder | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral artery dissection | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 7 / 948 (0.74%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 1 / 2 | 6 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 6 / 948 (0.63%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 6 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 6 / 972 (0.62%) | 1 / 948 (0.11%) | 5 / 758 (0.66%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 8 / 972 (0.82%) | 11 / 948 (1.16%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 13 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive emergency | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 6 / 948 (0.63%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iliac artery occlusion | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intermittent claudication | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 5 / 972 (0.51%) | 5 / 948 (0.53%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral embolism | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Temporal arteritis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 5 / 948 (0.53%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac death | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Chest discomfort | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 14 / 972 (1.44%) | 15 / 948 (1.58%) | 15 / 758 (1.98%) |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 15 | 0 / 17 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 8 / 972 (0.82%) | 5 / 948 (0.53%) | 6 / 758 (0.79%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 5 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 8 | 0 / 5 | 0 / 6 |
| Device related thrombosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug effect increased | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site haematoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injection site haematoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device site haematoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 1 / 948 (0.11%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Puncture site haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |
| Sudden death | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 7 / 948 (0.74%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 7 | 0 / 1 |
| Ulcer | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular stent occlusion | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular stent restenosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 5 / 972 (0.51%) | 3 / 948 (0.32%) | 4 / 758 (0.53%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular stent stenosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular stent thrombosis | | | |
| subjects affected / exposed | 25 / 972 (2.57%) | 17 / 948 (1.79%) | 10 / 758 (1.32%) |
| occurrences causally related to treatment / all | 4 / 25 | 2 / 17 | 2 / 10 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | 1 / 2 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 972 (0.41%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 3 / 948 (0.32%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Asthma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiectasis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 5 / 972 (0.51%) | 6 / 948 (0.63%) | 6 / 758 (0.79%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 8 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 11 / 972 (1.13%) | 17 / 948 (1.79%) | 10 / 758 (1.32%) |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 18 | 0 / 11 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Dyspnoea at rest | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 9 / 948 (0.95%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 2 / 3 | 9 / 11 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 5 / 948 (0.53%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 3 / 4 | 5 / 5 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Laryngeal oedema | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 8 / 972 (0.82%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 7 / 972 (0.72%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 4 / 758 (0.53%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination, visual | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paranoia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient psychosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Anticoagulation drug level above therapeutic | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Blood creatinine increased subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood pressure abnormal subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood pressure increased subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood urine subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood urine present subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematocrit decreased subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoglobin decreased subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 4 / 758 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 9 / 948 (0.95%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 8 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test increased | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Occult blood positive | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arterial bypass occlusion | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chemical burn | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusion postoperative | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 5 / 948 (0.53%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iatrogenic injury | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laceration | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament injury | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Near drowning | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural myocardial infarction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative fever | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative renal failure | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative thrombosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural complication | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skull fractured base | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic injury | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sternal fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular pseudoaneurysm | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 3 / 948 (0.32%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Generalised resistance to thyroid hormone | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phimosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous angioma of brain | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 4 / 948 (0.42%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|------------------|------------------|------------------|
| Acute left ventricular failure subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction subjects affected / exposed | 20 / 972 (2.06%) | 15 / 948 (1.58%) | 14 / 758 (1.85%) |
| occurrences causally related to treatment / all | 1 / 21 | 0 / 16 | 2 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Acute right ventricular failure subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris subjects affected / exposed | 20 / 972 (2.06%) | 18 / 948 (1.90%) | 18 / 758 (2.37%) |
| occurrences causally related to treatment / all | 1 / 22 | 0 / 20 | 1 / 21 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable subjects affected / exposed | 26 / 972 (2.67%) | 13 / 948 (1.37%) | 15 / 758 (1.98%) |
| occurrences causally related to treatment / all | 2 / 31 | 0 / 17 | 0 / 16 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve disease subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve disease mixed subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve incompetence subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve stenosis | | | |

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|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 44 / 972 (4.53%) | 34 / 948 (3.59%) | 36 / 758 (4.75%) |
| occurrences causally related to treatment / all | 0 / 51 | 0 / 41 | 0 / 44 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 18 / 972 (1.85%) | 6 / 948 (0.63%) | 8 / 758 (1.06%) |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 8 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block second degree | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradyarrhythmia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 5 / 972 (0.51%) | 6 / 948 (0.63%) | 5 / 758 (0.66%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 5 / 948 (0.53%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 1 / 4 | 0 / 1 |
| Cardiac asthma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 48 / 972 (4.94%) | 46 / 948 (4.85%) | 30 / 758 (3.96%) |
| occurrences causally related to treatment / all | 0 / 56 | 0 / 57 | 0 / 41 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 7 / 972 (0.72%) | 4 / 948 (0.42%) | 5 / 758 (0.66%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 7 / 972 (0.72%) | 3 / 948 (0.32%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 14 / 972 (1.44%) | 19 / 948 (2.00%) | 13 / 758 (1.72%) |
| occurrences causally related to treatment / all | 0 / 18 | 0 / 30 | 0 / 26 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| Cardiac flutter | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 6 / 972 (0.62%) | 7 / 948 (0.74%) | 6 / 758 (0.79%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 7 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed | 4 / 972 (0.41%) | 3 / 948 (0.32%) | 12 / 758 (1.58%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Heart valve incompetence | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Intracardiac thrombus | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microvascular coronary artery disease | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve prolapse | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 5 / 972 (0.51%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial fibrosis | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 5 / 948 (0.53%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 17 / 972 (1.75%) | 8 / 948 (0.84%) | 8 / 758 (1.06%) |
| occurrences causally related to treatment / all | 2 / 17 | 1 / 8 | 1 / 8 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis constrictive | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 3 / 948 (0.32%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Silent myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus arrest | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 5 / 972 (0.51%) | 3 / 948 (0.32%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systolic dysfunction | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 5 / 758 (0.66%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tricuspid valve incompetence | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trifascicular block | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricle rupture | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 7 / 972 (0.72%) | 3 / 948 (0.32%) | 5 / 758 (0.66%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 5 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal ganglia haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Basal ganglia stroke | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain injury | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain stem infarction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid arteriosclerosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid sinus syndrome | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 4 / 948 (0.42%) | 4 / 758 (0.53%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 4 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 1 |
| Dementia | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diplegia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disturbance in attention | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drop attacks | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalomalacia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Headache | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 1 / 948 (0.11%) | 4 / 758 (0.53%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar infarction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lateral medullary syndrome | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental impairment | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Movement disorder | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Quadripareisis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal claudication | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 9 / 972 (0.93%) | 7 / 948 (0.74%) | 10 / 758 (1.32%) |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 7 | 0 / 16 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tension headache | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 972 (0.62%) | 7 / 948 (0.74%) | 7 / 758 (0.92%) |
| occurrences causally related to treatment / all | 4 / 6 | 3 / 7 | 4 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia macrocytic | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Normochromic normocytic anaemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vestibular disorder | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Blindness transient | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 972 (0.21%) | 3 / 948 (0.32%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glaucoma | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 2 / 948 (0.21%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neovascular age-related macular degeneration | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric polyps | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 9 / 972 (0.93%) | 13 / 948 (1.37%) | 5 / 758 (0.66%) |
| occurrences causally related to treatment / all | 9 / 9 | 13 / 14 | 7 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal polyp haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal tract irritation | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 2 / 948 (0.21%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated inguinal hernia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 4 / 948 (0.42%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 3 / 4 | 3 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 4 / 948 (0.42%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 4 / 4 | 4 / 4 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Rectal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomach mass | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary cirrhosis primary | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 4 / 948 (0.42%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cholelithiasis | | | |
| subjects affected / exposed | 4 / 972 (0.41%) | 3 / 948 (0.32%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder perforation | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage subcutaneous | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stasis dermatitis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 15 / 972 (1.54%) | 6 / 948 (0.63%) | 14 / 758 (1.85%) |
| occurrences causally related to treatment / all | 2 / 15 | 0 / 6 | 1 / 18 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Acute prerenal failure | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Calculus bladder | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 7 / 948 (0.74%) | 4 / 758 (0.53%) |
| occurrences causally related to treatment / all | 2 / 3 | 7 / 7 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cyst | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 6 / 972 (0.62%) | 2 / 948 (0.21%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 3 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 972 (0.31%) | 1 / 948 (0.11%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal infarct | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal mass | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Thyroid mass | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bursitis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chondropathy | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Exostosis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 3 / 948 (0.32%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 7 / 972 (0.72%) | 2 / 948 (0.21%) | 4 / 758 (0.53%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteochondrosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plica syndrome | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polymyalgia rheumatica | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sacroiliitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone abscess | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 2 / 948 (0.21%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Candida infection | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 3 / 948 (0.32%) | 6 / 758 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot infection | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epididymitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fungal oesophagitis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gangrene | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis viral | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Helicobacter infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 3 / 948 (0.32%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orchitis | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 20 / 972 (2.06%) | 19 / 948 (2.00%) | 15 / 758 (1.98%) |
| occurrences causally related to treatment / all | 0 / 22 | 0 / 19 | 1 / 19 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia mycoplasmal | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal abscess | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scrotal abscess | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 972 (0.21%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 5 / 972 (0.51%) | 4 / 948 (0.42%) | 5 / 758 (0.66%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Skin bacterial infection | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic infection | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 972 (0.62%) | 4 / 948 (0.42%) | 3 / 758 (0.40%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 972 (0.21%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 972 (0.10%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 4 / 948 (0.42%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperhomocysteinaemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 2 / 758 (0.26%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 0 / 948 (0.00%) | 1 / 758 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 972 (0.21%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 972 (0.31%) | 1 / 948 (0.11%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic disorder | | | |
| subjects affected / exposed | 0 / 972 (0.00%) | 2 / 948 (0.21%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic syndrome | | | |
| subjects affected / exposed | 1 / 972 (0.10%) | 0 / 948 (0.00%) | 0 / 758 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Dabigatran Etexilate 110mg | Warfarin | Dabigatran Etexilate 150mg |
|---|-------------------------------|--------------------|-------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 128 / 972 (13.17%) | 229 / 948 (24.16%) | 126 / 758 (16.62%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 27 / 972 (2.78%) | 60 / 948 (6.33%) | 24 / 758 (3.17%) |
| occurrences (all) | 30 | 74 | 28 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 62 / 972 (6.38%) | 61 / 948 (6.43%) | 60 / 758 (7.92%) |
| occurrences (all) | 80 | 89 | 77 |
| Epistaxis | | | |

| | | | |
|-----------------------------|------------------|--------------------|------------------|
| subjects affected / exposed | 52 / 972 (5.35%) | 146 / 948 (15.40%) | 59 / 758 (7.78%) |
| occurrences (all) | 71 | 218 | 81 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 16 September 2015 | This amendment introduced several changes to facilitate patient recruitment and to operationally simplify trial procedures. The time windows for Visit 1 and for drug administration post PCI were prolonged (Visit 1 prolonged by 2 d and first drug administration prolonged by 48 h to a maximum of 120 h after PCI). It was allowed to use of blood samples taken by standard of care local laboratory up to 7 d prior to screening to verify eligibility. The physical examination was streamlined. A possibility to switch the antiplatelet therapy to ASA (≤ 100 mg once daily) after Month 12 as per investigator discretion was introduced as well. Inclusion/exclusion criteria were modified to allow inclusion of patients with atrial fibrillation secondary to a reversible disorder if they were candidates for long term oral anticoagulation; patients on cytotoxic/myelosuppressive therapy were no longer excluded. A clarification regarding the definition of active liver disease was added to the exclusion criterion 13. The use of the reversal agent for dabigatran was introduced as well as the allowance to collect the information regarding its use. The restriction of ASA use during the on-treatment period and recording of concomitant therapy throughout the trial were clarified. Subclassifications of myocardial infarction were introduced and the definitions of fatal and disabling stroke were added. Finally, the need for monitoring of drug-induced liver injury (AESIs) was removed as there were no signs of dabigatran-related hepatotoxicity during the clinical development and post-marketing period. |
| 05 April 2016 | This amendment revised the trial design due to insufficient patient recruitment rate. The trial focused on safety and was powered to test the non-inferiority of each of the dabigatran etexilate doses (110 mg and 150 mg bid) in a dual antithrombotic regimen versus warfarin in a triple antithrombotic regimen in respect to bleeding events (time to first ISTH major bleeding or clinically relevant non-major bleeding event). Efficacy parameters (e.g. all death, myocardial infarction, stroke/systemic embolism), including the original co-primary endpoint (DTE), were to be evaluated as secondary endpoints. A definition of unplanned revascularisation was added as well. Regarding hypothesis testing, a hierarchical approach replaced the original Benjamini-Hochberg procedure as the Type I error rate control method. The change of trial design led to the reduction of total number of entered patients from 8520 to 2502 and from 2840 entered patients per treatment arm to 834. Moreover, an unblinded interim analysis was removed to reflect the changes in trial design. Following the changes introduced by Global Amendment 1, the guideline on using the reversal agent was updated to reflect current approval status of idarucizumab. Finally, the amendment introduced that warfarin tablets were also supplied as blister packs. |
| 21 July 2016 | This amendment introduced that repeated revascularisation by PCI/CABG had to be adjudicated by the IAC as requested by the DMC. This change in administrative aspect did not require approval by the IRB/IEC/competent authority. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1 subject with missing information for number of enrolled subjects has been included in age range 'Elderly 85 years and over' as the missing category is not available.

Notes: