



Clinical trial results:

Phase 3 Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of Bococizumab (PF-04950615), in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects

Summary

| | |
|--------------------------|---|
| EudraCT number | 2013-002646-36 |
| Trial protocol | GB NL FI DE HU CZ SE SK ES IT BE DK PL IE |
| Global end of trial date | 22 March 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 02 June 2018 |
| First version publication date | 10 November 2017 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | B1481022 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01975376 |
| WHO universal trial number (UTN) | U1111-1151-0594 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 September 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 March 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superior efficacy of bococizumab compared with placebo in reducing the risk of major CV events, a composite endpoint which included adjudicated and confirmed CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina with urgent revascularization, in subjects at high or very high risk of major CV events who were on background lipid-lowering treatment and had an LDL-C ≥ 70 mg/dL (1.81 mmol/L) or non-HDL-C ≥ 100 mg/dL (2.59 mmol/L).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines and all local regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 29 October 2013 |
| 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: 776 |
| Country: Number of subjects enrolled | Australia: 165 |
| Country: Number of subjects enrolled | Belgium: 166 |
| Country: Number of subjects enrolled | Brazil: 1553 |
| Country: Number of subjects enrolled | Canada: 482 |
| Country: Number of subjects enrolled | Chile: 104 |
| Country: Number of subjects enrolled | China: 338 |
| Country: Number of subjects enrolled | Colombia: 228 |
| Country: Number of subjects enrolled | Czech Republic: 310 |
| Country: Number of subjects enrolled | Denmark: 328 |
| Country: Number of subjects enrolled | Finland: 281 |
| Country: Number of subjects enrolled | France: 190 |
| Country: Number of subjects enrolled | Germany: 1029 |
| Country: Number of subjects enrolled | Hungary: 413 |
| Country: Number of subjects enrolled | Ireland: 8 |
| Country: Number of subjects enrolled | Israel: 278 |
| Country: Number of subjects enrolled | Italy: 71 |
| Country: Number of subjects enrolled | Korea, Republic of: 104 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Mexico: 367 |
| Country: Number of subjects enrolled | Netherlands: 1016 |
| Country: Number of subjects enrolled | New Zealand: 113 |
| Country: Number of subjects enrolled | Poland: 1486 |
| Country: Number of subjects enrolled | Puerto Rico: 28 |
| Country: Number of subjects enrolled | Romania: 186 |
| Country: Number of subjects enrolled | Russian Federation: 415 |
| Country: Number of subjects enrolled | Slovakia: 439 |
| Country: Number of subjects enrolled | South Africa: 453 |
| Country: Number of subjects enrolled | Spain: 482 |
| Country: Number of subjects enrolled | Sweden: 272 |
| Country: Number of subjects enrolled | Switzerland: 64 |
| Country: Number of subjects enrolled | Taiwan: 49 |
| Country: Number of subjects enrolled | Thailand: 41 |
| Country: Number of subjects enrolled | Turkey: 47 |
| Country: Number of subjects enrolled | United Kingdom: 654 |
| Country: Number of subjects enrolled | United States: 3848 |
| Worldwide total number of subjects | 16784 |
| EEA total number of subjects | 7331 |

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) | 8994 |
| From 65 to 84 years | 7715 |
| 85 years and over | 75 |

Subject disposition

Recruitment

Recruitment details:

The trial was terminated prematurely on November 1, 2016, due to the emerging clinical profile and the evolving treatment and market landscape for lipid-lowering agents.

Pre-assignment

Screening details:

Study was conducted at multiple sites from 29 October 2013 to 22 March 2017. However, subjects were screened from 29 October 2013 through 01 November 2016.

Period 1

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

Arms

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

Arm description:

Subjects received single dose of placebo matched to PF-04950615 subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose.

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Matched to PF-04950615 subcutaneous injection once in every 2 Weeks for up to 3 years.

| | |
|------------------|---------------------------|
| Arm title | Bococizumab (PF-04950615) |
|------------------|---------------------------|

Arm description:

Subjects received single dose of PF-04950615 150 milligrams, subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bococizumab |
| Investigational medicinal product code | PF-04950615 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

150 milligrams, subcutaneous injection once in every 2 Weeks for up to 3 years.

| Number of subjects in period 1 | Placebo | Bococizumab (PF-04950615) |
|---------------------------------------|---------|---------------------------|
| Started | 8390 | 8394 |
| Received treatment | 8374 | 8386 |
| Completed | 8169 | 8179 |
| Not completed | 221 | 215 |
| Adverse event, serious fatal | 65 | 72 |
| Adverse event, non-fatal | 6 | 5 |
| Unspecified | 8 | 8 |
| Lost to follow-up | 70 | 66 |
| Withdrew consent | 72 | 64 |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received single dose of placebo matched to PF-04950615 subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose. | |
| Reporting group title | Bococizumab (PF-04950615) |
| Reporting group description: | |
| Subjects received single dose of PF-04950615 150 milligrams, subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose. | |

| Reporting group values | Placebo | Bococizumab (PF-04950615) | Total |
|--|---------|---------------------------|-------|
| Number of subjects | 8390 | 8394 | 16784 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 4496 | 4498 | 8994 |
| From 65-84 years | 3853 | 3862 | 7715 |
| 85 years and over | 41 | 34 | 75 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 63.3 | 63.3 | |
| standard deviation | ± 9.2 | ± 9.1 | - |
| Gender, Male/Female | | | |
| Units: Subjects | | | |
| Female | 2223 | 2207 | 4430 |
| Male | 6167 | 6187 | 12354 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1758 | 1746 | 3504 |
| Not Hispanic or Latino | 6631 | 6642 | 13273 |
| Unknown or Not Reported | 1 | 6 | 7 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 354 | 369 | 723 |
| Black or African American | 392 | 412 | 804 |
| White | 7315 | 7280 | 14595 |
| Unknown or Not Reported | 329 | 333 | 662 |

End points

End points reporting groups

| | |
|---|---------------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received single dose of placebo matched to PF-04950615 subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose. | |
| Reporting group title | Bococizumab (PF-04950615) |
| Reporting group description: | |
| Subjects received single dose of PF-04950615 150 milligrams, subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose. | |

Primary: Event Rate Per 100 Subject-Years For First Occurrence of Major Cardiovascular (CV) Event

| | |
|---|--|
| End point title | Event Rate Per 100 Subject-Years For First Occurrence of Major Cardiovascular (CV) Event |
| End point description: | |
| Event rate per 100 Subject-years for first occurrence of major CV event (adjudicated by Adjudication Committee) was reported. Major CV event was defined as any of the following: CV death (defined as sudden cardiac death, fatal myocardial infarction [MI], death due to heart failure, death due to stroke [fatal ischemic stroke or fatal stroke of undetermined etiology], or death due to other cardiovascular causes) non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization. Event rate was calculated as the number of events per 100 Subject-years at risk. Full analysis set (FAS): all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline until the date of first adjudicated and confirmed occurrence of major CV event (maximum duration: up to 3.4 years). | |

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events Per 100 Subject-Years | | | | |
| number (confidence interval 95%) | 3.02 (2.59 to 3.51) | 3.01 (2.58 to 3.50) | | |

Statistical analyses

| | |
|--|-------------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| Hazard ratio and 95 percent (%) Confidence Interval (CI) were from a Cox proportional hazards model stratified by geographic region and Low density lipoprotein cholesterol (LDL-C) at pre-screening (less than [$<$] 100 milligrams per deciliters [mg/dL], greater than and equal to [\geq] 100 mg/dL) with treatment as a co-variate. | |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.930905 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.22 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of Cardiovascular Death, Non-Fatal Myocardial Infraction, or Non-Fatal Stroke

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of Cardiovascular Death, Non-Fatal Myocardial Infraction, or Non-Fatal Stroke |
|-----------------|---|

End point description:

Cardiovascular death is defined as sudden cardiac death, fatal MI, death due to heart failure, death due to stroke [fatal ischemic stroke or fatal stroke of undetermined etiology], or death due to other cardiovascular causes). Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of the cardiovascular death, non-fatal MI or non-fatal stroke (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 2.49 (2.10 to 2.93) | 2.59 (2.19 to 3.04) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.784265 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.3 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of All-Cause Death, Non-Fatal Myocardial Infraction, Non-Fatal Stroke, or Hospitalization for Unstable Angina Needing Urgent Revascularization

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of All-Cause Death, Non-Fatal Myocardial Infraction, Non-Fatal Stroke, or Hospitalization for Unstable Angina Needing Urgent Revascularization |
|-----------------|--|

End point description:

Event rate per 100 Subject-years for first occurrence of composite endpoint of all-cause death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina needing urgent revascularization (adjudicated by Adjudication Committee) was reported. All-cause death was defined as the death due to any cause during the course of study. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of all-cause death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina needing urgent revascularization (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 3.51 (3.04 to 4.03) | 3.48 (3.02 to 4.00) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|---|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.892441 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.2 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of All-Cause Death, Non-Fatal Myocardial Infarction, or Non-Fatal Stroke

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of All-Cause Death, Non-Fatal Myocardial Infarction, or Non-Fatal Stroke |
|-----------------|--|

End point description:

Event rate per 100 participant-years for first occurrence of composite endpoint of all-cause death, non-fatal MI, or non-fatal stroke (adjudicated by Adjudication Committee) was reported. All-cause death was defined as the death due to any cause during the course of study. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of the all-cause death, non-fatal MI, or non-fatal stroke (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 2.98 (2.55 to 3.46) | 3.06 (2.62 to 3.54) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.845797 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.26 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Hospitalization for Unstable Angina Needing Urgent Revascularization

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of Hospitalization for Unstable Angina Needing Urgent Revascularization |
|-----------------|---|

End point description:

Event rate per 100 participant-years for first occurrence of hospitalization for unstable angina needing urgent revascularization (adjudicated by Adjudication Committee) was reported. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of hospitalization for unstable angina needing urgent revascularization (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.57 (0.39 to 0.80) | 0.47 (0.31 to 0.68) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.431903 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.36 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of Cardiovascular Death, Non-Fatal Myocardial Infarction, Non-Fatal Stroke and Hospitalization for Unstable Angina

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Composite Endpoint of Cardiovascular Death, Non-Fatal Myocardial Infarction, Non-Fatal Stroke and Hospitalization for Unstable Angina |
|-----------------|--|

End point description:

Event rate per 100 participant-years for first occurrence of composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina (adjudicated by Adjudication Committee) was reported. Cardiovascular death was defined as sudden cardiac death, fatal MI, death due to heart failure, death due to stroke (fatal ischemic stroke or fatal stroke of undetermined etiology), or death due to other cardiovascular causes. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of cardiovascular death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 3.22 (2.77 to 3.72) | 3.19 (2.74 to 3.69) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|---|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.883797 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.21 |

Secondary: Event rate per 100 Subject-years For Cardiovascular Death

| | |
|--|---|
| End point title | Event rate per 100 Subject-years For Cardiovascular Death |
| End point description: | |
| Event rate per 100 participant-years for cardiovascular death (adjudicated by Adjudication Committee) was reported. Cardiovascular death was defined as sudden cardiac death, fatal MI, death due to heart failure, death due to stroke (fatal ischemic stroke or fatal stroke of undetermined etiology), or death due to other cardiovascular causes. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline until the date of adjudicated and confirmed occurrence of cardiovascular death (maximum duration: up to 3.4 years) | |

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.52 (0.35 to 0.74) | 0.64 (0.45 to 0.88) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate. | |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.45569 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.95 |

Secondary: Event rate per 100 Subject-years For First Occurrence of any Myocardial Infarction (Fatal or Non-Fatal)

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of any Myocardial Infarction (Fatal or Non-Fatal) |
|-----------------|---|

End point description:

Event rate per 100 participant-years for first occurrence of any MI (Fatal or Non-Fatal) (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of any MI (fatal or non-fatal) (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 1.56 (1.26 to 1.92) | 1.74 (1.41 to 2.11) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.469496 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.48 |

Secondary: Event rate per 100 Subject-years For Fatal Myocardial Infarction

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For Fatal Myocardial Infarction |
|-----------------|--|

End point description:

Event rate per 100 participant-years for fatal MI (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of adjudicated and confirmed occurrence of fatal MI (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.03 (0.00 to 0.12) | 0.05 (0.01 to 0.15) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.633022 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.26 |
| upper limit | 9.23 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Non-Fatal Myocardial Infarction

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Non-Fatal Myocardial Infarction |
|-----------------|--|

End point description:

Event rate per 100 participant-years for first occurrence of non-fatal MI (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of non-fatal MI (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 1.53 (1.23 to 1.88) | 1.70 (1.38 to 2.07) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46765 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.48 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Any Stroke (Fatal or Non-Fatal)

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Any Stroke (Fatal or Non-Fatal) |
|-----------------|--|

End point description:

Event rate per 100 participant-years for first occurrence of any stroke (fatal or non-fatal) (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of any stroke (fatal or non-fatal) (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.71 (0.51 to 0.96) | 0.38 (0.24 to 0.57) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.015462 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 0.89 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Any Stroke (Fatal or Non-Fatal), of Any Etiology

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of Any Stroke (Fatal or Non-Fatal), of Any Etiology |
|-----------------|---|

End point description:

Event rate per 100 participant-years for first occurrence of any stroke (fatal or non-fatal), of any etiology (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of any stroke (fatal or non-fatal), of any etiology (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.79 (0.58 to 1.06) | 0.43 (0.28 to 0.64) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.011863 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 0.88 |

Secondary: Event rate per 100 Subject-years For Fatal Stroke

| | |
|------------------------|---|
| End point title | Event rate per 100 Subject-years For Fatal Stroke |
| End point description: | Event rate per 100 participant-years for fatal stroke (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. |
| End point type | Secondary |
| End point timeframe: | From baseline until the date of first adjudicated and confirmed occurrence of fatal stroke (maximum duration: up to 3.4 years) |

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.10 (0.04 to 0.22) | 0.05 (0.01 to 0.15) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate. |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.316066 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.12 |
| upper limit | 2 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Non-Fatal Stroke

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of Non-Fatal Stroke |
|-----------------|---|

End point description:

Event rate per 100 participant-years for first occurrence of non-fatal stroke (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of non-fatal stroke (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.62 (0.44 to 0.86) | 0.33 (0.20 to 0.51) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.020328 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 0.91 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Hospitalization for Unstable Angina

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Hospitalization for Unstable Angina |
|-----------------|--|

End point description:

Event rate per 100 participant-years for first occurrence of hospitalization for unstable angina (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of hospitalization for unstable angina (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.78 (0.57 to 1.04) | 0.64 (0.45 to 0.88) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.367069 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 1.27 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Hospitalization for Congestive Heart Failure (CHF)

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of Hospitalization for Congestive Heart Failure (CHF) |
|-----------------|---|

End point description:

Event rate per 100 participant-years for first occurrence of hospitalization for CHF (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of hospitalization for congestive heart failure (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.81 (0.60 to 1.08) | 0.69 (0.49 to 0.94) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.443081 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.29 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Coronary Revascularization

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of Coronary Revascularization |
|-----------------|---|

End point description:

Event rate per 100 participant-years for first occurrence of coronary revascularization (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of coronary revascularization (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 2.74 (2.33 to 3.20) | 2.45 (2.06 to 2.89) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.343817 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.12 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Coronary Artery Bypass Graft Surgery (CABG)

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Coronary Artery Bypass Graft Surgery (CABG) |
|-----------------|--|

End point description:

Event rate per 100 participant-years for first occurrence of CABG (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of CABG (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 0.40 (0.25 to 0.60) | 0.41 (0.26 to 0.61) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.889065 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.85 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Percutaneous Coronary Intervention (PCI)

| | |
|-----------------|---|
| End point title | Event rate per 100 Subject-years For First Occurrence of Percutaneous Coronary Intervention (PCI) |
|-----------------|---|

End point description:

Event rate per 100 participant-years for first occurrence of PCI (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of PCI (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 2.37 (1.99 to 2.80) | 2.08 (1.73 to 2.49) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.308388 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.13 |

Secondary: Event rate per 100 Subject-years For First Occurrence of Any Arterial Revascularizations

| | |
|-----------------|--|
| End point title | Event rate per 100 Subject-years For First Occurrence of Any Arterial Revascularizations |
|-----------------|--|

End point description:

Event rate per 100 participant-years for first occurrence of any arterial revascularizations (adjudicated by Adjudication Committee) was reported. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified.

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

End point timeframe:

From baseline until the date of first adjudicated and confirmed occurrence of any arterial revascularizations (maximum duration: up to 3.4 years)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 1.26 (0.99 to 1.59) | 1.28 (1.00 to 1.61) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate.

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.874835 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.42 |

Secondary: Event rate per 100 Subject-years For All-Cause Death

| | |
|--|--|
| End point title | Event rate per 100 Subject-years For All-Cause Death |
| End point description: | |
| Event rate per 100 participant-years for all-cause death (adjudicated by Adjudication Committee) was reported. All-cause death was defined as the death due to any cause during the course of study. Event rate was calculated as the number of events per 100 subject-years at risk. FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline until the date of adjudicated and confirmed occurrence of all-cause death (maximum duration: up to 3.4 years) | |

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|---------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Events per 100 Subject-years | | | | |
| number (confidence interval 95%) | 1.00 (0.76 to 1.29) | 1.13 (0.88 to 1.44) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| Hazard ratio and 95% CI were from a Cox proportional hazards model stratified by geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL) with treatment as a covariate. | |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |

| | |
|---|-------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.526269 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.6 |

Secondary: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Week 14

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Week 14 |
|-----------------|--|

End point description:

FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. Here, "Number of subjects analyzed "(N) signifies those subjects who were evaluable for this outcome measure.

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

End point timeframe:

Baseline, Week 14

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|-----------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6448 | 6439 | | |
| Units: Percent change | | | | |
| least squares mean (standard error) | 3.40 (± 0.31) | -57.17 (± 0.31) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Least Square (LS)- mean differences, associated 95% CI, and p-values were from a mixed model repeated measures (MMRM) model including observations through Week 70 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL).

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 12887 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-mean difference |
| Point estimate | -60.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -61.43 |
| upper limit | -59.71 |

Secondary: Nominal Change From Baseline in Low Density Lipoprotein Cholesterol at Week 14

| | |
|-----------------|--|
| End point title | Nominal Change From Baseline in Low Density Lipoprotein Cholesterol at Week 14 |
|-----------------|--|

End point description:

FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. Here, "N" signifies number of subjects who were evaluable for this outcome measure.

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

End point timeframe:

Baseline, Week 14

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|-----------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6448 | 6439 | | |
| Units: mg/dL | | | | |
| least squares mean (standard error) | 2.33 (± 0.28) | -52.37 (± 0.28) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

LS- mean differences and associated 95% CI, and p-values were from an MMRM model including observations through Week 70 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL).

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 12887 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-mean difference |
| Point estimate | -54.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -55.48 |
| upper limit | -53.92 |

Secondary: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Last Post-Baseline Measurement

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Last Post-Baseline Measurement |
|-----------------|---|

End point description:

FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. Here, "N" signifies number of subjects who were evaluable for this outcome measure.

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

End point timeframe:

Baseline, last post-baseline measurement (any time up to Week 140)

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|-----------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8240 | 8254 | | |
| Units: Percent Change | | | | |
| least squares mean (standard error) | 5.05 (± 0.35) | -41.67 (± 0.35) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

LS- mean difference and associated 95% CI, and p-value were from an analysis of covariance (ANCOVA) model with fixed effects for treatment group, baseline value, geographic region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL).

| | |
|-------------------|-------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
|-------------------|-------------------------------------|

| | |
|---|--------------------|
| Number of subjects included in analysis | 16494 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS-mean difference |
| Point estimate | -46.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -47.68 |
| upper limit | -45.76 |

Secondary: Percent Change From Baseline in Lipid Levels at Week 14

| | |
|---|---|
| End point title | Percent Change From Baseline in Lipid Levels at Week 14 |
| End point description: | |
| Lipids included non-high density lipoprotein cholesterol (non-HDL-C), total cholesterol, very low density lipoprotein cholesterol (VLDL-C), remnant lipoprotein cholesterol (RLP-C), apolipoprotein B (Apo B), HDL-C and apolipoprotein A-I (Apo A-I). FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. Here, "n" signifies number of subjects who were evaluable at the specified categories for each arm respectively. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 14 | |

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|-------------------------------------|-----------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Percent Change | | | | |
| least squares mean (standard error) | | | | |
| Non-HDL-C (n=6427,6412) | 3.21 (± 0.28) | -51.66 (± 0.28) | | |
| Total cholesterol (n=6441, 6431) | 2.38 (± 0.20) | -34.13 (± 0.20) | | |
| VLDL-C (n=6443, 6433) | 6.52 (± 0.45) | -13.65 (± 0.45) | | |
| RLP-C (n=6418, 6400) | 9.23 (± 0.79) | -21.02 (± 0.79) | | |
| Apo B (n= 5887, 5894) | 2.80 (± 0.31) | -55.76 (± 0.31) | | |
| HDL-C (n= 6431, 6412) | 1.19 (± 0.16) | 7.33 (± 0.16) | | |
| Apo A-I (n= 5890, 5896) | 1.21 (± 0.18) | 4.74 (± 0.18) | | |

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| Non-HDL-C: LS- mean differences, associated 95% CI, and p-values were from an MMRM model including observations through Week 70 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL). | |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-mean difference |
| Point estimate | -54.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -55.66 |
| upper limit | -54.09 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| Total cholesterol: LS- mean differences, associated 95% CI, and p-values were from an MMRM model including observations through Week 70 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL). | |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-mean difference |
| Point estimate | -36.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -37.07 |
| upper limit | -35.95 |

| | |
|--|-------------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| VLDL-C: LS- mean differences, associated 95% CI, and p-values were from an MMRM model including observations through Week 70 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL). | |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-mean difference |
| Point estimate | -20.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.42 |
| upper limit | -18.93 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|-----------------------------------|--------------------------------|

Statistical analysis description:

RLP-C: LS- mean differences, associated 95% CI, and p-values were from an MMRM model including observations through Week 70 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL).

| | |
|---|---------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-Mean Difference |
| Point estimate | -30.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.44 |
| upper limit | -28.07 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|-----------------------------------|--------------------------------|

Statistical analysis description:

Apo B: LS -mean differences, associated 95% CI, and p-values were from an MMRM model including observations through Week 52 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL).

| | |
|---|---------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-Mean Difference |
| Point estimate | -58.55 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -59.42 |
| upper limit | -57.69 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|-----------------------------------|--------------------------------|

Statistical analysis description:

HDL-C: LS- mean differences, associated 95% CI, and p-values were from an MMRM model including observations through Week 70 with fixed effects for treatment group, visit, treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL).

| | |
|---|---------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-Mean Difference |
| Point estimate | 6.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.69 |
| upper limit | 6.59 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|-----------------------------------|--------------------------------|

Statistical analysis description:

Apo A-I: LS- mean differences, associated 95% CI, and p-values were from an MMRM model including observations through Week 52 with fixed effects for treatment group, visit,treatment group*visit interaction, baseline value, baseline value*visit interaction, geographic region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL).

| | |
|---|---------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-Mean Difference |
| Point estimate | 3.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.02 |
| upper limit | 4.03 |

Secondary: Percent Change From Baseline in Log-Transformed Lipoprotein (a) (Lp[a]) and Triglycerides at Week 14

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in Log-Transformed Lipoprotein (a) (Lp[a]) and Triglycerides at Week 14 |
|-----------------|--|

End point description:

FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. Here, "n" signifies number of subjects who were evaluable at the specified categories for each arm respectively.

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

End point timeframe:

Baseline, Week 14

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|--------------------------------------|-----------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8390 | 8394 | | |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Lp(a) (n=5914, 5916) | -1.3 (± 28.81) | -33.9 (± 29.62) | | |
| Triglycerides (n= 6443, 6433) | 0.6 (± 32.84) | -18.9 (± 28.44) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
|----------------------------|--------------------------------|

Statistical analysis description:

Lp (a): LS- mean differences and associated 95% CI, and p-values were from an MMRM model on the difference of log-transformed observations through Week 52 with fixed effects for treatment group, visit, treatment group*visit interaction, log-transformed baseline value, log-transformed baseline value*visit interaction, geographical region and LDL-C at pre-screening (<100 mg/dL, ≥100 mg/dL).

| | |
|---|--|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement (M |
| Parameter estimate | LS-mean difference |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 0.68 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| Triglycerides: LS- mean differences and associated 95% CI, and p-values were from an MMRM model through Week 70 on the difference of log-transformed observations with fixed effects for treatment group, visit, treatment group*visit interaction, log-transformed baseline value, log-transformed baseline value*visit interaction, geographical region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL). | |
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 16784 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-mean difference |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 0.81 |

Secondary: Percent Change From Baseline in Log-Transformed High Sensitivity C-Reactive Protein (hs-CRP) at Week 14

| | |
|--|--|
| End point title | Percent Change From Baseline in Log-Transformed High Sensitivity C- Reactive Protein (hs-CRP) at Week 14 |
| End point description: | |
| FAS: all subjects who were randomized, excluding who attempted to be randomized more than once into a bococizumab CV outcomes trial (B1481022/ B1481038) or attempted to be randomized in more than 1 CV outcomes trial and all subjects enrolled at study Site 3027 where a quality-related event was identified. Here, "N" signifies number of subjects who were evaluable for this outcome measure. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 14 | |

| End point values | Placebo | Bococizumab (PF-04950615) | | |
|--------------------------------------|-----------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5931 | 5930 | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | -6.5 (± 88.28) | -1.1 (± 91.91) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Placebo vs PF--04950615 150 mg |
| Statistical analysis description: | |
| LS- mean differences and associated 95% CI, and p-values were from an MMRM model on the difference of log-transformed observations through Week 52 with fixed effects for treatment group, visit, treatment group*visit interaction, log-transformed baseline value, log-transformed baseline value*visit | |

interaction, geographical region and LDL-C at pre-screening (<100 mg/dL, >=100 mg/dL).

| | |
|---|---------------------------------------|
| Comparison groups | Placebo v Bococizumab (PF-04950615) |
| Number of subjects included in analysis | 11861 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Effect Model Repeat Measurement |
| Parameter estimate | LS-mean difference |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 1.1 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 3.4 years

Adverse event reporting additional description:

Safety analysis set: all participants who randomized, had at least 1 dose of study drug, excluding those attempted to randomize more than once in a bococizumab CV outcomes trial (B1481022/B1481038) or attempted to randomize in more than 1 CV outcomes trial, and all participants enrolled at study Site 3027 where a quality-related event was identified

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Bococizumab (PF-04950615) |
|-----------------------|---------------------------|

Reporting group description:

Subjects received single dose of PF-04950615 150 milligrams, subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received single dose of placebo matched to PF-04950615 subcutaneous injection once in every 2 weeks for up to 3 years. Subjects were followed up to 40 days after the last dose.

| Serious adverse events | Bococizumab (PF-04950615) | Placebo | |
|---|---------------------------|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1060 / 8386 (12.64%) | 986 / 8374 (11.77%) | |
| number of deaths (all causes) | 72 | 65 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Adenocarcinoma of colon | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign gastrointestinal neoplasm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct cancer | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bladder cancer | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer recurrent | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder neoplasm | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder papilloma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder transitional cell carcinoma stage I | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone cancer | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer recurrent | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholesteatoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic myelomonocytic leukaemia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clear cell renal cell carcinoma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer metastatic | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer stage III | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric adenoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastrointestinal stromal tumour | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal tract adenoma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal cancer | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glioblastoma multiforme | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intestinal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraocular melanoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large cell lung cancer | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal cancer | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lip and/or oral cavity cancer stage 0 | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipoma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liposarcoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma metastatic | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung neoplasm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung squamous cell carcinoma stage III | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Maxillofacial sinus neoplasm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesothelioma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to bone | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lymph nodes | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to peritoneum | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to spine | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal neoplasm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroendocrine carcinoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal adenocarcinoma | | | |

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|---|--|-------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian adenoma | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[1] | 1 / 2206 (0.05%) | 0 / 2216 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic neoplasm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Prostate cancer | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[2] | 13 / 6180 (0.21%) | 12 / 6158 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 13 | 1 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer metastatic | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[3] | 1 / 6180 (0.02%) | 1 / 6158 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic adenoma | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[4] | 0 / 6180 (0.00%) | 1 / 6158 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal adenoma | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Renal cancer recurrent | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Soft tissue neoplasm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |

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|---|--|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the cervix | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[5] | 0 / 2206 (0.00%) | 1 / 2216 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsil cancer | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[6] | 1 / 2206 (0.05%) | 2 / 2216 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Accelerated hypertension | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aneurysm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 9 / 8374 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial stenosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteritis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brachiocephalic vein stenosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry gangrene | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism arterial | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral artery aneurysm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Granulomatosis with polyangiitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive emergency | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iliac artery occlusion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infarction | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intermittent claudication | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 11 / 8386 (0.13%) | 7 / 8374 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery dissection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 12 / 8386 (0.14%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 9 / 8386 (0.11%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 7 / 8374 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral venous disease | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post thrombotic syndrome | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian artery occlusion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian artery stenosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Hospitalisation | | | |

| | | | |
|--|--|-------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[7] | 1 / 2206 (0.05%) | 0 / 2216 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac death | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 15 / 8386 (0.18%) | 16 / 8374 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 15 / 8386 (0.18%) | 10 / 8374 (0.12%) | |
| occurrences causally related to treatment / all | 1 / 15 | 3 / 10 | |
| deaths causally related to treatment / all | 3 / 4 | 1 / 1 | |
| Electrocution | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperplasia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ill-defined disorder | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection site hypersensitivity | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Necrosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 45 / 8386 (0.54%) | 47 / 8374 (0.56%) | |
| occurrences causally related to treatment / all | 1 / 47 | 1 / 50 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic mass | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |

| | | | |
|---|--|------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent restenosis | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent thrombosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| Pregnancy of partner | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[8] | 1 / 6180 (0.02%) | 1 / 6158 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[9] | 1 / 6180 (0.02%) | 5 / 6158 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystocele | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[10] | 0 / 2206 (0.00%) | 1 / 2216 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fallopian tube obstruction | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[11] | 1 / 2206 (0.05%) | 0 / 2216 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital prolapse | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[12] | 1 / 2206 (0.05%) | 0 / 2216 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Menorrhagia | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[13] | 0 / 2206 (0.00%) | 1 / 2216 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[14] | 0 / 2206 (0.00%) | 1 / 2216 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic dysplasia | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[15] | 0 / 6180 (0.00%) | 1 / 6158 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic obstruction | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[16] | 1 / 6180 (0.02%) | 0 / 6158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Prostatitis | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[17] | 1 / 6180 (0.02%) | 1 / 6158 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatomegaly | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[18] | 0 / 6180 (0.00%) | 1 / 6158 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectocele | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[19] | 0 / 2206 (0.00%) | 1 / 2216 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[20] | 1 / 2206 (0.05%) | 0 / 2216 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine prolapse | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[21] | 0 / 2206 (0.00%) | 1 / 2216 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal haemorrhage | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[22] | 0 / 2206 (0.00%) | 1 / 2216 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal prolapse | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[23] | 1 / 2206 (0.05%) | 0 / 2216 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal ulceration | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[24] | 1 / 2206 (0.05%) | 0 / 2216 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|------------------|------------------|--|
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Asthma | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial disorder | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |

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|---|-------------------|-------------------|
| subjects affected / exposed | 22 / 8386 (0.26%) | 11 / 8374 (0.13%) |
| occurrences causally related to treatment / all | 0 / 23 | 0 / 11 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |
| Chronic respiratory failure | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Dyspnoea | | |
| subjects affected / exposed | 10 / 8386 (0.12%) | 13 / 8374 (0.16%) |
| occurrences causally related to treatment / all | 1 / 13 | 0 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Emphysema | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Epistaxis | | |
| subjects affected / exposed | 7 / 8386 (0.08%) | 2 / 8374 (0.02%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Haemoptysis | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hypoxia | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal disorder | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal turbinate hypertrophy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oropharyngeal swelling | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumomediastinum | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Sinus disorder | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcoholism | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Conversion disorder | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression suicidal | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Factitious disorder | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major depression | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Personality disorder | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device battery issue | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device dislocation | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stone | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary colic | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary dyskinesia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 8 / 8374 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystocholangitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-alcoholic fatty liver | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood glucose increased | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure decreased | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure diastolic decreased | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac stress test abnormal | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heart rate abnormal | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis C virus test positive | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio abnormal | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio decreased | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test increased | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress echocardiogram abnormal | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Anaemia postoperative | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial injury | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain herniation | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Burns second degree | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac function disturbance postoperative | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ventricle collapse | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest injury | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye injury | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 6 / 8386 (0.07%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Femoral neck fracture | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal anastomotic leak | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gun shot wound | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Heat exhaustion | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Humerus fracture | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mallet finger | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple injuries | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle rupture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle strain | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery restenosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post concussion syndrome | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural oedema | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative delirium | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative thoracic procedure complication | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural hypertension | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 7 / 8374 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Seroma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skull fracture | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal column injury | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tendon injury | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic intracranial haemorrhage | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ulna fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular bypass dysfunction | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava injury | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Hereditary haemorrhagic telangiectasia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 11 / 8386 (0.13%) | 8 / 8374 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 11 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 40 / 8386 (0.48%) | 29 / 8374 (0.35%) | |
| occurrences causally related to treatment / all | 3 / 42 | 0 / 31 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Angina pectoris | | | |
| subjects affected / exposed | 73 / 8386 (0.87%) | 52 / 8374 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 76 | 0 / 55 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 65 / 8386 (0.78%) | 84 / 8374 (1.00%) | |
| occurrences causally related to treatment / all | 2 / 73 | 0 / 90 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-------------------|-------------------|--|
| Aortic valve stenosis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 27 / 8386 (0.32%) | 32 / 8374 (0.38%) | |
| occurrences causally related to treatment / all | 1 / 29 | 0 / 42 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 9 / 8374 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |

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|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 7 / 8386 (0.08%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac discomfort | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorder | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 21 / 8386 (0.25%) | 19 / 8374 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 23 | 0 / 20 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 24 / 8386 (0.29%) | 32 / 8374 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 27 | 1 / 40 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 4 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 30 / 8386 (0.36%) | 31 / 8374 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 31 | 0 / 32 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Coronary artery dissection | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heart valve incompetence | | | |

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|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microvascular coronary artery disease | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 35 / 8386 (0.42%) | 32 / 8374 (0.38%) | |
| occurrences causally related to treatment / all | 1 / 37 | 1 / 34 | |
| deaths causally related to treatment / all | 0 / 7 | 1 / 2 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 6 / 8386 (0.07%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 6 / 8386 (0.07%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 9 / 8374 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Axonal neuropathy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal ganglia haemorrhage | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem infarction | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid arteriosclerosis | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery disease | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 14 / 8386 (0.17%) | 8 / 8374 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral artery occlusion | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral venous thrombosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chorea | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cubital tunnel syndrome | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embololic stroke | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paresis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic cerebral infarction | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraventricular haemorrhage | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 20 / 8386 (0.24%) | 28 / 8374 (0.33%) | |
| occurrences causally related to treatment / all | 1 / 21 | 0 / 31 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lacunar stroke | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nerve compression | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post stroke epilepsy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 17 / 8386 (0.20%) | 13 / 8374 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 17 | 1 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thalamus haemorrhage | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 21 / 8386 (0.25%) | 19 / 8374 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 21 | 0 / 19 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular dementia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo CNS origin | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 8386 (0.07%) | 8 / 8374 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemorrhagic anaemia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eustachian tube dysfunction | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vestibular disorder | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lens dislocation | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular fibrosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic ischaemic neuropathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal exudates | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia obstructive | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 7 / 8374 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal polyp | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal prolapse | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendix disorder | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic gastritis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic pseudo-obstruction | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Constipation | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal haemorrhagic | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastric perforation | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric polyps | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroduodenitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal polyp haemorrhage | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hiatus hernia | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated umbilical hernia | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 10 / 8386 (0.12%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal strangulation | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |

| | | |
|---|------------------|------------------|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Melaena | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Necrotising colitis | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Obstruction gastric | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Oesophageal spasm | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Oesophageal stenosis | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Oesophagitis | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Pancreatitis | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 5 / 8386 (0.06%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer perforation | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal polyp | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary gland enlargement | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Short-bowel syndrome | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal stenosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis mesenteric vessel | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tongue oedema | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcerative gastritis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cutaneous vasculitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decubitus ulcer | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Petechiae | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoriasis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin reaction | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 14 / 8386 (0.17%) | 18 / 8374 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Calculus urethral | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic nephropathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephritis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 6 / 8386 (0.07%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephropathy | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal artery stenosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cortical necrosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal disorder | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal ischaemia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stag horn calculus | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral obstruction | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid mass | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 6 / 8386 (0.07%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Arthropathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone lesion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Costochondritis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic arthropathy | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gouty arthritis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc degeneration | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 6 / 8374 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Knee deformity | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle tightness | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 10 / 8386 (0.12%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 22 / 8386 (0.26%) | 18 / 8374 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 22 | 0 / 19 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteolysis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 6 / 8386 (0.07%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal column stenosis | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigger finger | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess neck | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 7 / 8374 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 8 / 8374 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis infective | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis infective staphylococcal | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carbuncle | | | |

| | | | |
|---|--|-------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 11 / 8386 (0.13%) | 13 / 8374 (0.16%) | |
| occurrences causally related to treatment / all | 1 / 11 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis of male external genital organ | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[25] | 1 / 6180 (0.02%) | 0 / 6158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium colitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Creutzfeldt-Jakob disease | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermo-hypodermatitis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot infection | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 7 / 8374 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Emphysematous pyelonephritis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis bacterial | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis enterococcal | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometritis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Furuncle | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis viral | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 9 / 8374 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis bacterial | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin abscess | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haematoma infection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis E | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incision site infection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected bite | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected fistula | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected seroma | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lyme disease | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 8 / 8386 (0.10%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis bacterial | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis chronic | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Penile infection | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periodontitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|--|-------------------|--|
| subjects affected / exposed | 34 / 8386 (0.41%) | 39 / 8374 (0.47%) | |
| occurrences causally related to treatment / all | 1 / 34 | 0 / 41 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural cellulitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural pneumonia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic abscess | Additional description: This is gender specific event. | | |
| subjects affected / exposed ^[26] | 0 / 6180 (0.00%) | 1 / 6158 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyomyositis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal abscess | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 7 / 8386 (0.08%) | 8 / 8374 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 3 | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Skin candida | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superinfection | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheobronchitis | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 15 / 8386 (0.18%) | 13 / 8374 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 3 / 8386 (0.04%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral sepsis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Visceral leishmaniasis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 7 / 8386 (0.08%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes with hyperosmolarity | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 8386 (0.00%) | 4 / 8374 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 2 / 8374 (0.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 5 / 8386 (0.06%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 3 / 8374 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperosmolar hyperglycaemic state | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypervolaemia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 8386 (0.02%) | 5 / 8374 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 3 / 8386 (0.04%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Insulin-requiring type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ketoacidosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 8386 (0.00%) | 1 / 8374 (0.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obesity | | | |

| | | |
|---|------------------|------------------|
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Type 2 diabetes mellitus | | |
| subjects affected / exposed | 4 / 8386 (0.05%) | 4 / 8374 (0.05%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Vitamin B12 deficiency | | |
| subjects affected / exposed | 1 / 8386 (0.01%) | 0 / 8374 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The event is gender specific event, hence number of subjects at risk are not equal to the total number of subjects.

| Non-serious adverse events | Bococizumab (PF-04950615) | Placebo | |
|---|---------------------------|----------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2015 / 8386 (24.03%) | 1570 / 8374 (18.75%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 270 / 8386 (3.22%) | 303 / 8374 (3.62%) | |
| occurrences (all) | 280 | 317 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 171 / 8386 (2.04%) | 136 / 8374 (1.62%) | |
| occurrences (all) | 189 | 160 | |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 588 / 8386 (7.01%) | 88 / 8374 (1.05%) | |
| occurrences (all) | 1949 | 188 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 169 / 8386 (2.02%) | 133 / 8374 (1.59%) | |
| occurrences (all) | 197 | 157 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 208 / 8386 (2.48%) | 197 / 8374 (2.35%) | |
| occurrences (all) | 224 | 224 | |
| Back pain | | | |
| subjects affected / exposed | 217 / 8386 (2.59%) | 203 / 8374 (2.42%) | |
| occurrences (all) | 227 | 211 | |
| Myalgia | | | |
| subjects affected / exposed | 170 / 8386 (2.03%) | 160 / 8374 (1.91%) | |
| occurrences (all) | 186 | 190 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 283 / 8386 (3.37%) | 289 / 8374 (3.45%) | |
| occurrences (all) | 317 | 308 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 183 / 8386 (2.18%) | 193 / 8374 (2.30%) | |
| occurrences (all) | 204 | 213 | |

| | | | |
|------------------------------------|--------------------|--------------------|--|
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 217 / 8386 (2.59%) | 195 / 8374 (2.33%) | |
| occurrences (all) | 217 | 196 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 01 October 2014 | 1. An efficacy endpoint of any stroke (fatal and non-fatal), of any etiology which included hemorrhagic stroke, was added. 2. More frequent visits for assessment of direct LDL-C and AEs/serious AEs, for subjects who have had investigational product dose frequency modifications to quater 4 week so that the data monitoring committee can monitor more closely, lipid levels in subjects with a history of low levels of LDL-C during the trial was added. 3. Depression assessments was added so as to capture baseline risk for the disorder, given that depression was found fairly frequently in subjects at high risk of cardiovascular events and its presence might alter performance on the planned cognitive assessments. 4. Health care utilization assessments and endpoints was added to evaluate the potential impact of bococizumab on health care resource utilization. 5. Screening laboratory tests, hs-CRP and Lp(a) was added for subjects who had not had a prior cardiovascular event, since these were established risk factors for the occurrence of cardiovascular events. 6. Safety section was modified to clarify further, how serious adverse events were to be reported. |
| 12 February 2016 | 1. Clinical secondary objectives and endpoints were updated to reflect an upgrading of the secondary endpoint of a composite endpoint of all-cause death, non-fatal MI and non-fatal stroke to a key secondary endpoint, in consideration of its clinical importance. The secondary endpoint of nominal change in hs-CRP was changed to percent change in hs-CRP. 2. The proposed indication was modified so that the major cardiovascular events reflected components of the primary endpoint. 3. The safety reporting section was revised to reflect the fact that a Pfizer internal serious adverse event triage group will ensure the correct reporting of serious AEs to the Pfizer Drug Safety Unit. 4. The cerebral hemorrhage risk exclusion was modified to clarify that a prior lacunar infarct refers to a prior lacunar stroke, ie, a lacunar infarct which resulted in a stroke. 5. An exclusion criterion of gastric bypass surgery was added, since its presence could complicate the interpretation of metabolic efficacy and safety data. 6. A requirement was added to the protocol that IP should not be administered, if a subject was prescribed a marketed proprotein convertase subtilisin/kexin type 9 inhibitor during the conduct of the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|--------------|
| 01 November 2016 | The trial was terminated prematurely on November 1, 2016, due to the emerging clinical profile and the evolving treatment and market landscape for lipid-lowering agents. These indicated that bococizumab was not likely to provide value to patients, physicians, or shareholders. The decision was not based on a recommendation by the independent Data Monitoring Committee to stop the program. | - |

Notes:

Limitations and caveats

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

As specified in SAP, due to discontinuation of the bococizumab clinical development program, health care resource utilization (HCRU) endpoints were not evaluated.

Notes: