



Clinical trial results:

A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination fluticasone furoate/umeclidinium/vilanterol, with the fixed dose dual combinations of fluticasone furoate/vilanterol and umeclidinium/vilanterol, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease

Summary

| | |
|--------------------------|--|
| EudraCT number | 2013-003075-35 |
| Trial protocol | NL FI PL SE DE AT CZ BE DK ES NO RO HR |
| Global end of trial date | 17 July 2017 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v2 (current) |
| This version publication date | 27 September 2018 |
| First version publication date | 22 July 2018 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 116855 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

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 | 19 October 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 July 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI), to reduce the annual rate of moderate and severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in participants with, chronic obstructive pulmonary disease (COPD).

Protection of trial subjects:

An Independent data monitoring committee (IDMC) reviewed unblinded safety data periodically throughout the trial to ensure participant safety.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 30 June 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 1085 |
| Country: Number of subjects enrolled | Australia: 256 |
| Country: Number of subjects enrolled | Austria: 130 |
| Country: Number of subjects enrolled | Belgium: 139 |
| Country: Number of subjects enrolled | Brazil: 143 |
| Country: Number of subjects enrolled | Canada: 309 |
| Country: Number of subjects enrolled | Chile: 434 |
| Country: Number of subjects enrolled | China: 669 |
| Country: Number of subjects enrolled | Colombia: 62 |
| Country: Number of subjects enrolled | Czech Republic: 150 |
| Country: Number of subjects enrolled | Denmark: 128 |
| Country: Number of subjects enrolled | Finland: 101 |
| Country: Number of subjects enrolled | France: 175 |
| Country: Number of subjects enrolled | Germany: 1408 |
| Country: Number of subjects enrolled | Hong Kong: 50 |
| Country: Number of subjects enrolled | Israel: 265 |
| Country: Number of subjects enrolled | Japan: 470 |
| Country: Number of subjects enrolled | Korea, Republic of: 424 |
| Country: Number of subjects enrolled | Netherlands: 367 |
| Country: Number of subjects enrolled | New Zealand: 103 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Norway: 122 |
| Country: Number of subjects enrolled | Peru: 253 |
| Country: Number of subjects enrolled | Philippines: 130 |
| Country: Number of subjects enrolled | Poland: 95 |
| Country: Number of subjects enrolled | Puerto Rico: 56 |
| Country: Number of subjects enrolled | Romania: 108 |
| Country: Number of subjects enrolled | Russian Federation: 368 |
| Country: Number of subjects enrolled | Singapore: 25 |
| Country: Number of subjects enrolled | South Africa: 365 |
| Country: Number of subjects enrolled | Spain: 654 |
| Country: Number of subjects enrolled | Sweden: 168 |
| Country: Number of subjects enrolled | Thailand: 174 |
| Country: Number of subjects enrolled | Turkey: 60 |
| Country: Number of subjects enrolled | Ukraine: 113 |
| Country: Number of subjects enrolled | United Kingdom: 292 |
| Country: Number of subjects enrolled | United States: 3936 |
| Country: Number of subjects enrolled | Vietnam: 118 |
| Worldwide total number of subjects | 13905 |
| EEA total number of subjects | 4037 |

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) | 6312 |
| From 65 to 84 years | 7476 |
| 85 years and over | 117 |

Subject disposition

Recruitment

Recruitment details:

Participants with chronic obstructive pulmonary disease (COPD), were randomized to the study. Study was conducted from 30 June 2014 to 17 July 2017, at total of 971 sites in 37 countries.

Pre-assignment

Screening details:

A total of 13,906 participants (par.) were registered for the study of which 13099 were screened (807 pre-screen failure) and 10,367 were randomized to the study (2744 screen failure). Of which 12 par. were randomized in error and 10,355 were randomized to actual treatment and included in Intent to treat (ITT) Population.

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 |

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | FF/UMEC/VI |

Arm description:

The eligible participants in this arm received Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI) as a fixed dose combination (FDC) as 100 microgram (μ cg)/62.5 μ cg/25 μ cg once daily (QD) via a dry powder inhaler (DPI), in the morning, for duration of 52 weeks.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fluticasone Furoate/Umeclidinium/Vilanterol Trifenatate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Administered as 100 μ cg/62.5 μ cg/25 μ cg, QD in morning via DPI for 52-weeks

| | |
|------------------|-------|
| Arm title | FF/VI |
|------------------|-------|

Arm description:

The eligible participants in this arm received FF/VI 100 μ cg/25 μ cg QD via DPI, in the morning for duration of 52 weeks.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Fluticasone furoate/ Vilanterol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Administered as 100 μ cg/25 μ cg, QD in morning via DPI for 52-weeks

| | |
|------------------|---------|
| Arm title | UMEC/VI |
|------------------|---------|

Arm description:

The eligible participants in this arm received UMEC/VI 62.5 μ cg/25 μ cg QD via DPI, in the morning for duration of 52 weeks.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--------------------------|
| Investigational medicinal product name | Umeclidinium/ Vilanterol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Administered as 62.5µcg/25µcg, QD in morning via DPI for 52-weeks

| Number of subjects in period 1^[1] | FF/UMEC/VI | FF/VI | UMEC/VI |
|---|---------------------|---------------------|---------------------|
| Started | 4151 | 4134 | 2070 |
| Completed Investigational Product (IP) | 3393 ^[2] | 3094 ^[3] | 1504 ^[4] |
| Not completed IP | 758 ^[5] | 1040 ^[6] | 566 ^[7] |
| Withdrew IP (WIP): Adverse event | 249 ^[8] | 325 ^[9] | 186 ^[10] |
| WIP: Lack of efficacy | 163 ^[11] | 313 ^[12] | 172 ^[13] |
| Withdrew IP: Protocol deviation | 32 ^[14] | 41 ^[15] | 19 ^[16] |
| WIP (Other): Stopping criteria reached | 4 ^[17] | 1 ^[18] | 2 ^[19] |
| WIP: Study closed/terminated | 5 ^[20] | 2 ^[21] | 5 ^[22] |
| WIP: Lost to follow-up | 21 ^[23] | 25 ^[24] | 14 ^[25] |
| WIP: Investigator discretion | 33 ^[26] | 36 ^[27] | 15 ^[28] |
| WIP: Withdrawal by participant | 250 ^[29] | 296 ^[30] | 153 ^[31] |
| WIP :Did not complete Study treatment | 1 ^[32] | 1 ^[33] | 0 ^[34] |
| Completed | 3714 | 3598 | 1775 |
| Not completed | 437 | 536 | 295 |
| Adverse event, serious fatal | 85 | 91 | 58 |
| Consent withdrawn by subject | 192 | 261 | 130 |
| Physician decision | 47 | 57 | 28 |
| Adverse event, non-fatal | 77 | 89 | 53 |
| Other: Reason not provided by site | 1 | - | - |
| Other: Study Closed or terminated | 5 | 2 | 4 |
| Lost to follow-up | 30 | 36 | 22 |

Notes:

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

Justification: This number indicates the number of participants with withdrawal from investigational product only.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

completed, minus those who left.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

[31] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

[32] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

[33] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

[34] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number indicates the number of participants with withdrawal from investigational product only.

Baseline characteristics

Reporting groups

| | |
|--|------------|
| Reporting group title | FF/UMEC/VI |
| Reporting group description: | |
| The eligible participants in this arm received Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI) as a fixed dose combination (FDC) as 100 microgram (µcg)/62.5µcg/25µcg once daily (QD) via a dry powder inhaler (DPI), in the morning, for duration of 52 weeks. | |
| Reporting group title | FF/VI |
| Reporting group description: | |
| The eligible participants in this arm received FF/VI 100µcg/25µcg QD via DPI, in the morning for duration of 52 weeks. | |
| Reporting group title | UMEC/VI |
| Reporting group description: | |
| The eligible participants in this arm received UMEC/VI 62.5µcg/25µcg QD via DPI, in the morning for duration of 52 weeks. | |

| Reporting group values | FF/UMEC/VI | FF/VI | UMEC/VI |
|------------------------|------------|-------|---------|
| Number of subjects | 4151 | 4134 | 2070 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|--------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 65.3 | 65.3 | 65.2 |
| standard deviation | ± 8.24 | ± 8.30 | ± 8.26 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1385 | 1386 | 714 |
| Male | 2766 | 2748 | 1356 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 87 | 86 | 45 |
| Asian - Central/South Asian Heritage | 6 | 3 | 1 |
| Asian - East Asian Heritage | 362 | 374 | 177 |
| Asian - Japanese Heritage | 151 | 152 | 82 |
| Asian - South East Asian Heritage | 149 | 147 | 75 |
| Black or African American | 122 | 99 | 43 |
| Native Hawaiian or other Pacific Islander | 2 | 3 | 2 |
| White - Arabic/North African Heritage | 31 | 45 | 24 |
| White - White/Caucasian/European Heritage | 3200 | 3179 | 1604 |
| Multiple | 41 | 45 | 17 |
| Unknown | 0 | 1 | 0 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 10355 | | |

| | | | |
|---|------|--|--|
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 3485 | | |
| Male | 6870 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaska Native | 218 | | |
| Asian - Central/South Asian Heritage | 10 | | |
| Asian - East Asian Heritage | 913 | | |
| Asian - Japanese Heritage | 385 | | |
| Asian - South East Asian Heritage | 371 | | |
| Black or African American | 264 | | |
| Native Hawaiian or other Pacific Islander | 7 | | |
| White - Arabic/North African Heritage | 100 | | |
| White - White/Caucasian/European Heritage | 7983 | | |
| Multiple | 103 | | |
| Unknown | 1 | | |

End points

End points reporting groups

| | |
|--|------------|
| Reporting group title | FF/UMEC/VI |
| Reporting group description: The eligible participants in this arm received Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI) as a fixed dose combination (FDC) as 100 microgram (µcg)/62.5µcg/25µcg once daily (QD) via a dry powder inhaler (DPI), in the morning, for duration of 52 weeks. | |
| Reporting group title | FF/VI |
| Reporting group description: The eligible participants in this arm received FF/VI 100µcg/25µcg QD via DPI, in the morning for duration of 52 weeks. | |
| Reporting group title | UMEC/VI |
| Reporting group description: The eligible participants in this arm received UMEC/VI 62.5µcg/25µcg QD via DPI, in the morning for duration of 52 weeks. | |

Primary: Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI and FF/VI

| | |
|--|---|
| End point title | Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI and FF/VI |
| End point description: The annual rate of moderate or severe COPD, exacerbations which occurred during treatment was assessed. Moderate exacerbations were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations were defined as exacerbations that required hospitalization or resulted in death. Analysis performed using a generalized linear model assuming a negative binomial distribution. ITT population was used which comprised of all randomized participants, excluding those who were randomized in error. Only those participants with non-missing co-variables were included in the analysis. | |
| End point type | Primary |
| End point timeframe: Up to Week 52 | |

| End point values | FF/UMEC/VI | FF/VI | UMEC/VI | |
|---|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4145 ^[1] | 4133 ^[2] | 2069 ^[3] | |
| Units: Exacerbations per participant per year | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Exacerbations per participant per year | 0.91 (0.87 to 0.95) | 1.07 (1.02 to 1.12) | 1.21 (1.14 to 1.29) | |

Notes:

[1] - ITT Population

[2] - ITT Population

[3] - ITT Population

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Covariates of treatment group, sex, exacerbation history (≤ 1 , ≥ 2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted Forced expiratory volume in 1 second (FEV1) (Screening) were used. | |
| Comparison groups | FF/UMEC/VI v UMEC/VI |
| Number of subjects included in analysis | 6214 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | < 0.001 |
| Method | Negative binomial model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 0.81 |

Notes:

[4] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons.

| | |
|--|----------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| Covariates of treatment group, sex, exacerbation history (≤ 1 , ≥ 2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted FEV1 (Screening) were used. | |
| Comparison groups | FF/VI v FF/UMEC/VI |
| Number of subjects included in analysis | 8278 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | < 0.001 |
| Method | Negative binomial model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 0.9 |

Notes:

[5] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons

Secondary: Change from Baseline in trough FEV1, at Week 52 comparing FF/UMEC/VI with FF/VI

| | |
|-----------------|--|
| End point title | Change from Baseline in trough FEV1, at Week 52 comparing FF/UMEC/VI with FF/VI ^[6] |
|-----------------|--|

End point description:

FEV1, was defined as the amount of air a person exhales in one second. Change from Baseline, was calculated as the value of FEV1 at Week 52 minus the value at Baseline. Baseline for trough FEV1 was defined as Day 1 (Pre-dose). Only those participants with non-missing co-variates were included in the analysis. The analysis was performed using a Repeated measures model with covariates of treatment group, smoking status (Screening), geographical region, visit, Baseline, Baseline by visit and treatment group by visit interactions.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 52 | |

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

| End point values | FF/UMEC/VI | FF/VI | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3366 ^[7] | 3060 ^[8] | | |
| Units: Liter | | | | |
| least squares mean (standard error) | | | | |
| Liter | 0.094 (± 0.0042) | -0.003 (± 0.0044) | | |

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Comparison groups | FF/VI v FF/UMEC/VI |
| Number of subjects included in analysis | 6426 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | < 0.001 |
| Method | Mixed Models Repeated Measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.097 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.085 |
| upper limit | 0.109 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0061 |

Notes:

[9] - The adjusted p-value at Week 52 should be compared against a reference level of 0.05 in order to infer statistical significance for the comparison of FF/UMEC/VI versus (vs) FF/VI at Week 52.

Secondary: Change from Baseline in St. George's Respiratory Questionnaire for (SGRQ) Total Score at Week 52 comparing FF/UMEC/VI with FF/VI

| | |
|-----------------|--|
| End point title | Change from Baseline in St. George's Respiratory Questionnaire for (SGRQ) Total Score at Week 52 comparing FF/UMEC/VI with FF/VI ^[10] |
|-----------------|--|

End point description:

SGRQ is a disease specific-questionnaire, designed to measure impact of respiratory disease and its treatment on a COPD participant's Health Related Quality of Life (HRQoL). SGRQ contains 14 questions with total of 40 items grouped into three domains (Symptoms, Activity, and Impacts). The overall summary score along with scores for the individual domains of symptoms, activity and impacts were assessed. Score was calculated by summing the pre-assigned weights of answers, dividing by sum of maximum weights for items in SGRQ. Total scores ranged from 0 to 100. A decrease in score indicates improvement in HRQoL and higher score implies worse quality of life. Change from Baseline was calculated as total score at Week 52 minus value at Baseline. Baseline was defined as Day 1. Minimum

clinically important difference (MCID) for this instrument is a 4-point improvement (decrease from Baseline). Only those participants with non-missing co-variables were included in the analysis.

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

End point timeframe:

Baseline and Week 52

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

| End point values | FF/UMEC/VI | FF/VI | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3318 ^[11] | 3026 ^[12] | | |
| Units: Scores on SGRQ scale | | | | |
| least squares mean (standard error) | | | | |
| Scores on SGRQ scale | -5.5 (± 0.23) | -3.7 (± 0.24) | | |

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Comparison groups | FF/VI v FF/UMEC/VI |
| Number of subjects included in analysis | 6344 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | < 0.001 |
| Method | Mixed Models Repeated Measures |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | -1.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.34 |

Notes:

[13] - The adjusted p-value at Week 52 should be compared against a reference level of 0.05 in order to infer statistical significance for the comparison of FF/UMEC/VI vs FF/VI at Week 52.

Secondary: Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI

| | |
|-----------------|--|
| End point title | Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI |
|-----------------|--|

End point description:

This measures the number of days, to first onset of moderate or severe exacerbations. Moderate exacerbations, were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations, were defined as exacerbations that required hospitalization or resulted in death. Hazard ratio from Cox proportional hazards model with covariates of treatment group, sex, exacerbation history (<=1, >=2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted FEV1 (Screening), have been reported. Only those participants with non-missing co-variables

were included in analysis. The first quartile and median time to onset, are taken from the Kaplan-Meier estimates. If <25% (and <50%) of participants experienced the event within a treatment then Q1 (and median) time to onset are displayed as 99999 which is not applicable for that treatment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 52 | |

| End point values | FF/UMEC/VI | FF/VI | UMEC/VI | |
|------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1959 ^[14] | 2039 ^[15] | 1036 ^[16] | |
| Units: Days | | | | |
| First quartile time to onset | 112 | 81 | 73 | |
| Median time to onset | 99999 | 99999 | 306 | |

Notes:

[14] - ITT population

[15] - ITT population

[16] - ITT population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|-------------------------------|
| Comparison groups | FF/UMEC/VI v FF/VI |
| Number of subjects included in analysis | 3998 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | < 0.001 |
| Method | Cox proportional hazard model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 0.91 |

Notes:

[17] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons.

| Statistical analysis title | Statistical analysis 2 |
|---|-------------------------------|
| Comparison groups | UMEC/VI v FF/UMEC/VI |
| Number of subjects included in analysis | 2995 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[18] |
| P-value | < 0.001 |
| Method | Cox proportional hazard model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 0.91 |

Notes:

[18] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons.

Secondary: Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of participants with a blood eosinophil count ≥ 150 cells per microliter

| | |
|-----------------|---|
| End point title | Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of participants with a blood eosinophil count ≥ 150 cells per microliter ^[19] |
|-----------------|---|

End point description:

The annual rate of moderate or severe COPD exacerbations during the treatment, for participants with blood eosinophil count ≥ 150 cells per microliter at Baseline, has been reported. Moderate exacerbations, were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations were defined as exacerbations that required hospitalization or resulted in death. Only those participants with non-missing co-variables and non-missing EOS at Baseline were included in the analysis.

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

End point timeframe:

Up to Week 52

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

| End point values | FF/UMEC/VI | UMEC/VI | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2296 ^[20] | 1195 ^[21] | | |
| Units: Exacerbations per participant per year | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Exacerbations per participant per year | 0.95 (0.90 to 1.01) | 1.39 (1.29 to 1.51) | | |

Notes:

[20] - ITT population

[21] - ITT population

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | FF/UMEC/VI v UMEC/VI |
| Number of subjects included in analysis | 3491 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Negative binomial Model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.68 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 0.75 |

Secondary: Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of participants with a blood eosinophil count ≥ 150 cells per microliter at Baseline

| | |
|-----------------|---|
| End point title | Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of participants with a blood eosinophil count ≥ 150 cells per microliter at Baseline ^[22] |
|-----------------|---|

End point description:

This measures the number of days, to the first onset of moderate or severe exacerbations for participants with blood eosinophil count ≥ 150 cells per microliter, at Baseline has been reported. Moderate exacerbations, were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations, were defined as exacerbations that required hospitalization or resulted in death. Only those participants with non-missing co-variables and non missing EOS at Baseline were included in the analysis. First quartile and median time to onset are taken from the Kaplan-Meier estimates. If $<25\%$ (and $<50\%$) of participants experienced the event within a treatment then Q1 (and median) time to onset are displayed as 99999, not applicable for that treatment.

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

End point timeframe:

Up to Week 52

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

| End point values | FF/UMEC/VI | UMEC/VI | | |
|------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2296 ^[23] | 1195 ^[24] | | |
| Units: Days | | | | |
| First quartile time to onset | 107 | 55 | | |
| Median time to onset | 99999 | 253 | | |

Notes:

[23] - ITT population

[24] - ITT population

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | UMEC/VI v FF/UMEC/VI |
| Number of subjects included in analysis | 3491 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Cox proportional hazard model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 0.85 |

Secondary: Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI

| | |
|--|---|
| End point title | Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI |
| End point description: | |
| The annual rate of severe COPD exacerbations during the treatment, has been reported. Severe exacerbations were defined as exacerbations that required hospitalization or resulted in death. The covariates of treatment group, sex, exacerbation history (≤ 1 , ≥ 2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted FEV1 (Screening) were used. Only those participants with non-missing co-variables were included in the analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 52 | |

| End point values | FF/UMEC/VI | FF/VI | UMEC/VI | |
|---|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4145 ^[25] | 4133 ^[26] | 2069 ^[27] | |
| Units: Exacerbations per participant per year | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Exacerbations per participant per year | 0.13 (0.12 to 0.14) | 0.15 (0.13 to 0.16) | 0.19 (0.17 to 0.22) | |

Notes:

[25] - ITT population

[26] - ITT population

[27] - ITT population

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | FF/VI v FF/UMEC/VI |
| Number of subjects included in analysis | 8278 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.064 |
| Method | Negative binomial model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.87 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.01 |

| | |
|---|-------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Comparison groups | FF/UMEC/VI v UMEC/VI |
| Number of subjects included in analysis | 6214 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Negative binomial model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.78 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment Serious adverse events (SAEs) and Adverse events (AEs) are reported from the first dose of randomized medication up to Week 52.

Adverse event reporting additional description:

All AEs and SAEs in the ITT Population were reported. The number of on-treatment deaths are reported from date of first dose of study medication up to the day after the last date of study medication.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | FF/UMEC/VI 100/62.5/25 |
|-----------------------|------------------------|

Reporting group description:

The eligible participants in this arm received FF/UMEC/VI as a FDC as 100 µcg/62.5µcg/25µcg, QD via a DPI, in the morning, for duration of 52 weeks.

| | |
|-----------------------|--------------|
| Reporting group title | FF/VI 100/25 |
|-----------------------|--------------|

Reporting group description:

The eligible participants in this arm received FF/VI 100µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.

| | |
|-----------------------|-----------------|
| Reporting group title | UMEC/VI 62.5/25 |
|-----------------------|-----------------|

Reporting group description:

The eligible participants in this arm received UMEC/VI 62.5µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.

| Serious adverse events | FF/UMEC/VI 100/62.5/25 | FF/VI 100/25 | UMEC/VI 62.5/25 |
|---|---------------------------|------------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 895 / 4151 (21.56%) | 850 / 4134 (20.56%) | 470 / 2070 (22.71%) |
| number of deaths (all causes) | 68 | 76 | 49 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign breast neoplasm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign fallopian tube neoplasm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 4 / 4134 (0.10%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bladder neoplasm | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder transitional cell carcinoma stage I | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone neoplasm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain neoplasm | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Colon cancer stage I | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epiglottic carcinoma | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibroma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal neoplasm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glottis carcinoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemangioma of spleen | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic angiosarcoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hepatic cancer metastatic | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hepatic neoplasm | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal cancer | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal squamous cell carcinoma | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma stage III | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Lung carcinoma cell type unspecified stage I | | | |

| | | | |
|---|------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung carcinoma cell type unspecified stage IV | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 6 / 4151 (0.14%) | 10 / 4134 (0.24%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 10 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Lung squamous cell carcinoma stage II | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm of ampulla of Vater | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm of unknown primary site | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|------------------|------------------|
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lymph nodes | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Monoclonal gammopathy | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine carcinoma | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour of the lung | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Oral neoplasm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pancreatic neoplasm | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papilloma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasma cell myeloma | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 4 / 4134 (0.10%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyogenic granuloma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sarcoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Small cell lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Small intestine carcinoma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue sarcoma | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the cervix | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the oral cavity | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Throat cancer | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsil cancer | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral cancer | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vulval cancer | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Acute aortic syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aneurysm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic aneurysm | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic aneurysm rupture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism arterial | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral artery aneurysm | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemodynamic instability | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive emergency | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iliac artery occlusion | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Peripheral venous disease | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicose ulceration | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Surgical and medical procedures | | | |
| Hernia repair | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------|------------------|------------------|
| Asthenia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 5 / 4151 (0.12%) | 3 / 4134 (0.07%) | 7 / 2070 (0.34%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complication associated with device | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Condition aggravated | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 5 / 4134 (0.12%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 2 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hernia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |

| | | | |
|---|------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Implant site fibrosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated hernia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device site haemorrhage | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 8 / 4151 (0.19%) | 10 / 4134 (0.24%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 10 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral swelling | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stent-graft endoleak | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| Sudden death | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 0 |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Allergy to arthropod sting | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Anaphylactic shock | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystocele | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | | |
|---|---------------------|---------------------|---------------------|--|
| Acute respiratory failure | | | | |
| subjects affected / exposed | 23 / 4151 (0.55%) | 17 / 4134 (0.41%) | 16 / 2070 (0.77%) | |
| occurrences causally related to treatment / all | 2 / 27 | 1 / 17 | 0 / 20 | |
| deaths causally related to treatment / all | 1 / 4 | 0 / 3 | 0 / 4 | |
| Asthma-chronic obstructive pulmonary disease overlap syndrome | | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Atelectasis | | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Bronchiectasis | | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Choking | | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 443 / 4151 (10.67%) | 450 / 4134 (10.89%) | 269 / 2070 (13.00%) | |
| occurrences causally related to treatment / all | 21 / 554 | 27 / 569 | 16 / 337 | |
| deaths causally related to treatment / all | 1 / 13 | 1 / 22 | 1 / 11 | |
| Chronic respiratory failure | | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 4151 (0.07%) | 4 / 4134 (0.10%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercapnia | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Lung disorder | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pickwickian syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleurisy | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |

| | | | |
|---|------------------|-------------------|------------------|
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 8 / 4151 (0.19%) | 11 / 4134 (0.27%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 2 / 13 | 0 / 12 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 5 / 4151 (0.12%) | 5 / 4134 (0.12%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 7 / 4151 (0.17%) | 7 / 4134 (0.17%) | 6 / 2070 (0.29%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 7 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 3 |
| Pulmonary granuloma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hilum mass | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary infarction | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory acidosis | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Respiratory distress | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 22 / 4151 (0.53%) | 21 / 4134 (0.51%) | 7 / 2070 (0.34%) |
| occurrences causally related to treatment / all | 1 / 23 | 3 / 21 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 3 | 1 / 4 | 0 / 1 |
| Psychiatric disorders | | | |
| Affective disorder | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alcoholism | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 4 / 4134 (0.10%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Insomnia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Major depression | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychotic disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Substance-induced psychotic disorder | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Biopsy prostate | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood pressure increased | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibrin D dimer increased | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Occult blood positive | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatic specific antigen increased | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcus test positive | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin increased | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Animal bite | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chemical peritonitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Chest injury | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Comminuted fracture | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conjunctival laceration | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body aspiration | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder postoperative | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Heat illness | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 4 / 4151 (0.10%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Muscle rupture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haematuria | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural stroke | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative respiratory failure | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural complication | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 9 / 4151 (0.22%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seroma | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin injury | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue injury | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic rupture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress fracture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound evisceration | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Developmental hip dysplasia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial bridging | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Odontogenic cyst | | | |

| | | | |
|---|-------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 13 / 4151 (0.31%) | 8 / 4134 (0.19%) | 6 / 2070 (0.29%) |
| occurrences causally related to treatment / all | 1 / 14 | 1 / 8 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 3 / 4134 (0.07%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 7 / 4151 (0.17%) | 6 / 4134 (0.15%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 6 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis coronary artery | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 21 / 4151 (0.51%) | 13 / 4134 (0.31%) | 6 / 2070 (0.29%) |
| occurrences causally related to treatment / all | 4 / 24 | 3 / 13 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| Atrial flutter | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular dissociation | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 3 / 4151 (0.07%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 12 / 4151 (0.29%) | 7 / 4134 (0.17%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 8 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 21 / 4151 (0.51%) | 12 / 4134 (0.29%) | 7 / 2070 (0.34%) |
| occurrences causally related to treatment / all | 0 / 28 | 1 / 12 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Cardiac valve disease | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 4 / 4151 (0.10%) | 4 / 4134 (0.10%) | 5 / 2070 (0.24%) |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 4 | 1 / 4 | 0 / 5 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cor pulmonale | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cor pulmonale chronic | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 2 / 4134 (0.05%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery insufficiency | | | |

| | | | |
|---|-------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 10 / 4151 (0.24%) | 6 / 4134 (0.15%) | 7 / 2070 (0.34%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 6 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 5 / 4151 (0.12%) | 1 / 4134 (0.02%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prinzmetal angina | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus arrest | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachyarrhythmia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ataxia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain stem ischaemia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain stem stroke | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar infarction | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral amyloid angiopathy | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cerebral infarction | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 4151 (0.07%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 7 / 4151 (0.17%) | 6 / 4134 (0.15%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 7 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Guillain-Barre syndrome | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 5 / 4134 (0.12%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Lacunar infarction | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental impairment | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral nerve paresis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radicular syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Simple partial seizures | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 6 / 4151 (0.14%) | 5 / 4134 (0.12%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Tension headache | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thalamic infarction | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 8 / 4151 (0.19%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 4 / 4134 (0.10%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic disorder | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Microcytic anaemia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Meniere's disease | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vestibular disorder | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Amaurosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 5 / 4134 (0.12%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract nuclear | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal compartment syndrome | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal distension | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 4 / 4134 (0.10%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erosive duodenitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erosive oesophagitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric polyps | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer perforation | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 4 / 4134 (0.10%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated umbilical hernia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 6 / 4151 (0.14%) | 4 / 4134 (0.10%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Intestinal polyp | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 2 / 4134 (0.05%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic cyst | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic failure | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritoneal haemorrhage | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal fibrosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 4151 (0.07%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 5 / 2070 (0.24%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder perforation | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder polyp | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decubitus ulcer | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathic ulcer | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peau d'orange | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pustular psoriasis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 6 / 4151 (0.14%) | 9 / 4134 (0.22%) | 6 / 2070 (0.29%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 9 | 0 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Bladder disorder | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder stenosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| End stage renal disease | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephropathy | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstructive uropathy | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Renal aneurysm | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cyst haemorrhage | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 4151 (0.07%) | 3 / 4134 (0.07%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vesicocutaneous fistula | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal mass | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|------------------|------------------|
| Back pain | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone infarction | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Costochondritis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoroacetabular impingement | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin pain | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 3 / 4134 (0.07%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 4 / 4134 (0.10%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 9 / 4151 (0.22%) | 5 / 4134 (0.12%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporosis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal deformity | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal ligament ossification | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebral foraminal stenosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendiceal abscess | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspergillus infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 10 / 4151 (0.24%) | 10 / 4134 (0.24%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 11 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carbuncle | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 6 / 4151 (0.14%) | 1 / 4134 (0.02%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridial infection | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic abscess | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Corona virus infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 3 / 4134 (0.07%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis bacterial | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis infectious | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis infectious | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fungal oesophagitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gangrene | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 5 / 4134 (0.12%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| H1N1 influenza | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Haemophilus infection | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Helicobacter infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected varicose vein | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Infection | | | |

| | | | |
|---|------------------|-------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of bronchiectasis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 8 / 4151 (0.19%) | 19 / 4134 (0.46%) | 7 / 2070 (0.34%) |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 20 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 7 / 4151 (0.17%) | 6 / 4134 (0.15%) | 5 / 2070 (0.24%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 6 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Kidney infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 7 / 4151 (0.17%) | 4 / 4134 (0.10%) | 4 / 2070 (0.19%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis viral | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mycobacterial infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mycoplasma infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nosocomial infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Oesophageal candidiasis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral infection | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orchitis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis acute | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parotitis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngotonsillitis | | | |

| | | | |
|---|--------------------|--------------------|-------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumococcal sepsis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 184 / 4151 (4.43%) | 152 / 4134 (3.68%) | 54 / 2070 (2.61%) |
| occurrences causally related to treatment / all | 36 / 198 | 20 / 165 | 12 / 55 |
| deaths causally related to treatment / all | 0 / 10 | 0 / 5 | 0 / 3 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 9 / 4134 (0.22%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 3 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia necrotising | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 3 / 4134 (0.07%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 9 / 4151 (0.22%) | 8 / 4134 (0.19%) | 6 / 2070 (0.29%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 8 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 2 / 4134 (0.05%) | 3 / 2070 (0.14%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Sinusitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subacute endocarditis | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdiaphragmatic abscess | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superinfection | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Tonsillitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 7 / 4134 (0.17%) | 4 / 2070 (0.19%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 7 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Acetonaemia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 4 / 4151 (0.10%) | 5 / 4134 (0.12%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 1 / 4134 (0.02%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid overload | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 0 / 4134 (0.00%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 3 / 4151 (0.07%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 7 / 4151 (0.17%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 4151 (0.12%) | 1 / 4134 (0.02%) | 2 / 2070 (0.10%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 2 / 4151 (0.05%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obesity | | | |
| subjects affected / exposed | 1 / 4151 (0.02%) | 0 / 4134 (0.00%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 2 / 4134 (0.05%) | 1 / 2070 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 4151 (0.00%) | 1 / 4134 (0.02%) | 0 / 2070 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | FF/UMEC/VI 100/62.5/25 | FF/VI 100/25 | UMEC/VI 62.5/25 |
|--|---------------------------|-------------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1389 / 4151 (33.46%) | 1278 / 4134 (30.91%) | 596 / 2070 (28.79%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 233 / 4151 (5.61%) | 197 / 4134 (4.77%) | 101 / 2070 (4.88%) |
| occurrences (all) | 385 | 332 | 139 |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| disorders | | | |
| Cough | | | |
| subjects affected / exposed | 145 / 4151 (3.49%) | 117 / 4134 (2.83%) | 58 / 2070 (2.80%) |
| occurrences (all) | 168 | 128 | 75 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 146 / 4151 (3.52%) | 139 / 4134 (3.36%) | 83 / 2070 (4.01%) |
| occurrences (all) | 180 | 164 | 101 |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 520 / 4151 (12.53%) | 479 / 4134 (11.59%) | 222 / 2070 (10.72%) |
| occurrences (all) | 712 | 658 | 316 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 297 / 4151 (7.15%) | 283 / 4134 (6.85%) | 117 / 2070 (5.65%) |
| occurrences (all) | 401 | 383 | 162 |
| Oral candidiasis | | | |
| subjects affected / exposed | 161 / 4151 (3.88%) | 146 / 4134 (3.53%) | 41 / 2070 (1.98%) |
| occurrences (all) | 203 | 176 | 50 |
| Bronchitis | | | |
| subjects affected / exposed | 142 / 4151 (3.42%) | 120 / 4134 (2.90%) | 70 / 2070 (3.38%) |
| occurrences (all) | 165 | 152 | 83 |
| Pneumonia | | | |
| subjects affected / exposed | 121 / 4151 (2.91%) | 127 / 4134 (3.07%) | 41 / 2070 (1.98%) |
| occurrences (all) | 131 | 135 | 43 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 31 March 2014 | Clarified approval status of products in the protocol, added wording concerning hematology collection, and corrected minor errors in the Time and Events Table |
| 10 April 2014 | Added post-bronchodilator FEV1 to each visit and included this as an other efficacy endpoint. A mortality endpoint was also added as an other efficacy endpoint. Other changes included changing the predicted FEV1 reference values from NHANES III to the European Respiratory Society Global Lung Function Initiative and to correct minor errors in CAT, contraceptive methods, and ECG wording. |
| 05 December 2014 | Clarified that SAEs in China would be recorded from the time the consent form was signed until the 7-day safety follow-up visit/telephone contact had been completed, or until Visit 7 (telephone contact) for participant who discontinued study treatment but continued in the study |
| 12 May 2015 | Clarified that none of the study sites in China would participate in genetic research in this study and addition of a China-specific sub-study to collect the unit-cost data for healthcare utilization among participants recruited in China. |
| 30 June 2016 | Simplified the statistical hierarchy for the analysis of secondary endpoints. In addition, there were minor changes to the definitions of the analysis populations, changes in model terms that were included in the primary efficacy endpoint analysis, and clarification on the primary endpoint sensitivity analysis. For the safety analysis, there were minor changes to clarify the analyses of Pneumonia AEs and Major Adverse Cardiac Events (MACE) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported