# Clinical trial results:
# A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD. [DYNAGITO]

## Summary

| | |
|---|---|
| EudraCT number | 2014-002275-28 |
| Trial protocol | FI IT SE PT DK BE NL HU GB ES AT IE LT CZ LV SK DE SI GR BG HR PL |
| Global end of trial date | 29 March 2017 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 11 January 2022 |
| First version publication date | 13 April 2018 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 1237.19 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02296138 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 12 May 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 March 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 March 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The overall objective was to assess the effect of once daily tiotropium + olodaterol fixed-dose combination compared to 5 µg tiotropium (both delivered with the RESPIMAT inhaler) on moderate to severe COPD exacerbation in patients with severe to very severe COPD.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded.

Background therapy: -

Evidence for comparator:

Approved Tiotropium inhalation solution - Respimat® inhaler

| | |
|---|---|
| Actual start date of recruitment | 13 January 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | South Africa: 118 |
| Country: Number of subjects enrolled | Spain: 230 |
| Country: Number of subjects enrolled | Sweden: 44 |
| Country: Number of subjects enrolled | Switzerland: 34 |
| Country: Number of subjects enrolled | Taiwan: 26 |
| Country: Number of subjects enrolled | Thailand: 69 |
| Country: Number of subjects enrolled | Turkey: 216 |
| Country: Number of subjects enrolled | Ukraine: 250 |
| Country: Number of subjects enrolled | United Kingdom: 65 |
| Country: Number of subjects enrolled | United States: 1241 |
| Country: Number of subjects enrolled | Vietnam: 41 |
| Country: Number of subjects enrolled | Hong Kong: 15 |
| Country: Number of subjects enrolled | Argentina: 348 |
| Country: Number of subjects enrolled | Australia: 98 |
| Country: Number of subjects enrolled | Austria: 61 |

| | |
|---|---|
| Country: Number of subjects enrolled | Belgium: 63 |
| Country: Number of subjects enrolled | Brazil: 173 |
| Country: Number of subjects enrolled | Bulgaria: 137 |
| Country: Number of subjects enrolled | Canada: 293 |
| Country: Number of subjects enrolled | Chile: 40 |
| Country: Number of subjects enrolled | Colombia: 30 |
| Country: Number of subjects enrolled | Croatia: 50 |
| Country: Number of subjects enrolled | Czechia: 152 |
| Country: Number of subjects enrolled | Denmark: 85 |
| Country: Number of subjects enrolled | Finland: 41 |
| Country: Number of subjects enrolled | France: 95 |
| Country: Number of subjects enrolled | Germany: 615 |
| Country: Number of subjects enrolled | Greece: 72 |
| Country: Number of subjects enrolled | Guatemala: 109 |
| Country: Number of subjects enrolled | Hungary: 226 |
| Country: Number of subjects enrolled | India: 336 |
| Country: Number of subjects enrolled | Ireland: 23 |
| Country: Number of subjects enrolled | Italy: 195 |
| Country: Number of subjects enrolled | Japan: 619 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 124 |
| Country: Number of subjects enrolled | Latvia: 60 |
| Country: Number of subjects enrolled | Lithuania: 41 |
| Country: Number of subjects enrolled | Malaysia: 52 |
| Country: Number of subjects enrolled | Mexico: 60 |
| Country: Number of subjects enrolled | Netherlands: 187 |
| Country: Number of subjects enrolled | New Zealand: 110 |
| Country: Number of subjects enrolled | Norway: 64 |
| Country: Number of subjects enrolled | Philippines: 126 |
| Country: Number of subjects enrolled | Poland: 528 |
| Country: Number of subjects enrolled | Portugal: 82 |
| Country: Number of subjects enrolled | Romania: 125 |
| Country: Number of subjects enrolled | Russian Federation: 958 |
| Country: Number of subjects enrolled | Serbia: 145 |
| Country: Number of subjects enrolled | Singapore: 7 |
| Country: Number of subjects enrolled | Slovakia: 81 |
| Country: Number of subjects enrolled | Slovenia: 49 |
| Worldwide total number of subjects | 9009 |
| EEA total number of subjects | 3306 |

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) | 3626 |

| | |
|---|---|
| From 65 to 84 years | 5284 |
| 85 years and over | 99 |

## Subject disposition

### Recruitment

Recruitment details:

A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD.

### Pre-assignment

Screening details:

Following informed consent, the patient was entered into a maximum 7-day screening period to confirm the patient's eligibility. At Visit 2, after a successful review of the inclusion and exclusion criteria, the patient was randomly allocated in equal ratio to receive once daily trial treatment and then entered the 360 days treatment phase.

### Period 1

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

Blinding implementation details:

A randomised, double-blind, active-controlled parallel group study

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Tiotropium 5 microgram (µg) |

Arm description:

Patient received 5 µg Tiotropium inhalation solution – RESPIMAT inhaler once daily orally for 360 days. One patient was not treated and 10 patients were found with data irregularities.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Oral use |

Dosage and administration details:

5 µg Tiotropium inhalation solution – RESPIMAT inhaler once daily orally for 360 days

| | |
|---|---|
| **Arm title** | Tiotropium (5 µg) + Olodaterol (5 µg) |

Arm description:

Patient received 5 µg Tiotropium + 5 µg Olodaterol fixed-dose combination (FDC) inhalation solution – RESPIMAT inhaler once daily orally for 360 days. One patient was not treated and 11 patients were found with data irregularities.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Tiotropium (5 µg) / Olodaterol (5 µg)_FDC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Oral use |

Dosage and administration details:

5 µg Tiotropium + 5 µg Olodaterol fixed-dose combination (FDC) inhalation solution – RESPIMAT inhaler once daily orally for 360 days

| **Number of subjects in period 1[1]** | Tiotropium 5 microgram (µg) | Tiotropium (5 µg) + Olodaterol (5 µg) |
|---|---|---|
| Started | 3941 | 3939 |
| Completed | 3291 | 3451 |
| Not completed | 650 | 488 |
| Adverse event, serious fatal | 83 | 82 |
| Consent withdrawn by subject | 184 | 131 |
| Adverse event, non-fatal | 265 | 177 |
| Other than specified | 15 | 13 |
| Lost to follow-up | 9 | 12 |
| Lack of efficacy | 59 | 37 |
| Protocol deviation | 35 | 36 |

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: Out of 9009 participants that were enrolled, only 7880 received the study medication.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Tiotropium 5 microgram (µg) |
| Reporting group description: | |
| Patient received 5 µg Tiotropium inhalation solution – RESPIMAT inhaler once daily orally for 360 days. One patient was not treated and 10 patients were found with data irregularities. | |
| Reporting group title | Tiotropium (5 µg) + Olodaterol (5 µg) |
| Reporting group description: | |
| Patient received 5 µg Tiotropium + 5 µg Olodaterol fixed-dose combination (FDC) inhalation solution – RESPIMAT inhaler once daily orally for 360 days. One patient was not treated and 11 patients were found with data irregularities. | |

| Reporting group values | Tiotropium 5 microgram (µg) | Tiotropium (5 µg) + Olodaterol (5 µg) | Total |
|---|---|---|---|
| Number of subjects | 3941 | 3939 | 7880 |
| Age categorical | | | |
| Treated set (TS): This patient set includes all randomised patients who were documented to have taken at least 1 dose of trial medication. | | | |
| Units: Subjects | | | |
| Age Continuous | | | |
| Age at the time of signing informed consent form is presented. Treated set (TS): This patient set includes all randomised patients who were documented to have taken at least 1 dose of trial medication. | | | |
| Units: years | | | |
| arithmetic mean | 66.3 | 66.5 | |
| standard deviation | ± 8.5 | ± 8.4 | - |
| Sex: Female, Male | | | |
| Number of subjects is categorized as Male or Female. Treated set (TS): This patient set includes all randomised patients who were documented to have taken at least 1 dose of trial medication. | | | |
| Units: Subjects | | | |
| Female | 1100 | 1154 | 2254 |
| Male | 2841 | 2785 | 5626 |
| Race (NIH/OMB) | | | |
| Ethnicity was not captured in this trial. Treated set (TS): This patient set includes all randomised patients who were documented to have taken at least 1 dose of trial medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 64 | 77 | 141 |
| Asian | 607 | 557 | 1164 |
| Native Hawaiian or Other Pacific Islander | 5 | 3 | 8 |
| Black or African American | 52 | 58 | 110 |
| White | 3113 | 3134 | 6247 |
| More than one race | 20 | 22 | 42 |
| Unknown or Not Reported | 80 | 88 | 168 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Tiotropium 5 microgram (µg) |
| Reporting group description: | |
| Patient received 5 µg Tiotropium inhalation solution – RESPIMAT inhaler once daily orally for 360 days. One patient was not treated and 10 patients were found with data irregularities. | |
| Reporting group title | Tiotropium (5 µg) + Olodaterol (5 µg) |
| Reporting group description: | |
| Patient received 5 µg Tiotropium + 5 µg Olodaterol fixed-dose combination (FDC) inhalation solution – RESPIMAT inhaler once daily orally for 360 days. One patient was not treated and 11 patients were found with data irregularities. | |

### Primary: Annualised rate of moderate to severe COPD exacerbations during the actual treatment period.

| | |
|---|---|
| End point title | Annualised rate of moderate to severe COPD exacerbations during the actual treatment period. |
| End point description: | |
| Annualised rate of moderate to severe COPD exacerbations during the actual treatment period was calculated per treatment per patient−year. The actual treatment period was defined as the interval from first in-take of study medication until 1 day after last in-take of study medication. Least Squares Means are actually exponentiated. Treated set (TS) -This patient set includes all randomised patients who were documented to have taken at least 1 dose of trial medication. | |
| End point type | Primary |
| End point timeframe: | |
| From first in-take of study medication until 1 day after last in-take of study medication, up to 361 days | |

| End point values | Tiotropium 5 microgram (µg) | Tiotropium (5 µg) + Olodaterol (5 µg) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3941[1] | 3939[2] | | |
| Units: Rate per patient−year | | | | |
| least squares mean (confidence interval 99%) | 0.97 (0.90 to 1.03) | 0.90 (0.84 to 0.96) | | |

Notes:

[1] - TS

[2] - TS

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Statistical analysis description: | |
| Annualised rate of moderate to severe COPD exacerbation was analysed using a negative binomial model including the fixed, categorical effect of treatment as well as the logarithm of the treatment exposure as an offset. | |
| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |

| | |
|---|---|
| Number of subjects included in analysis | 7880 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.0498 |
| Method | Negative binomial model |
| Parameter estimate | Ratio of rates vs. Tiotropium 5 µg |
| Point estimate | 0.93 |
| Confidence interval | |
| level | Other: 99 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.02 |

Notes:

[3] - This hypothesis testing strategy ensures that the overall type I error is protected at 2-sided 0.01 level. Ratio of events Tiotropium (5 µg) + Olodaterol (5 µg) versus Tiotropium (5 µg) is provided.

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

Statistical analysis description:

Model was based on HERMES- Covariates: age, sex, smoking status, baseline Long-acting Beta-agonist/inhaled corticosteroid, region and percent predicted post-bronchodilator Forced Expiratory Volume in One Second

| | |
|---|---|
| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |
| Number of subjects included in analysis | 7880 |
| Analysis specification | Post-hoc |
| Analysis type | superiority[4] |
| P-value | = 0.008 |
| Method | Negative binomial model |
| Parameter estimate | Ratio of rates |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 0.98 |

Notes:

[4] - Ratio of rates Tiotropium (5 µg) versus Tiotropium (5 µg) + Olodaterol (5 µg) is provided.

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|

Statistical analysis description:

Model was based on TRINITY/TRILOGY- Covariates: Treatment, region, severity of airflow limitation, and smoking status as effects, and exacerbations treated with antibiotics/steroids in previous year.

| | |
|---|---|
| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |
| Number of subjects included in analysis | 7880 |
| Analysis specification | Post-hoc |
| Analysis type | superiority[5] |
| P-value | = 0.0011 |
| Method | Negative binomial model |
| Parameter estimate | Ratio of rates |
| Point estimate | 0.89 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 0.96 |

Notes:

[5] - Ratio of rates Tiotropium (5 µg) versus Tiotropium (5 µg) + Olodaterol (5 µg) is provided.

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

Statistical analysis description:

Model was based on SPARK/FLAME- Covariates: Smoking status, baseline inhaled corticosteroid, Global Initiative on Chronic Obstructive Lung Disease stage, region, COPD Assessment Test score (replacing baseline symptom score), exacerbations treated with antibiotics/steroids history in previous year (replacing 1-year history of exacerbations)

| | |
|---|---|
| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |
| Number of subjects included in analysis | 7880 |
| Analysis specification | Post-hoc |
| Analysis type | superiority[6] |
| P-value | = 0.001 |
| Method | Negative binomial model |
| Parameter estimate | Ratio of rates |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 0.96 |

Notes:

[6] - Ratio of rates Tiotropium (5 µg) versus Tiotropium (5 µg) + Olodaterol (5 µg) is provided.

## Secondary: Time to first moderate to severe COPD exacerbation during the actual treatment period.

| End point title | Time to first moderate to severe COPD exacerbation during the actual treatment period. |
|---|---|

End point description:

Key secondary endpoint: Time to first moderate to severe COPD exacerbation during the actual treatment period per treatment. The actual treatment period was defined as the interval from first in-take of study medication until 1 day after last in-take of study medication. The median was not estimated due to less than 50% of patients having an event. Hence the number of patients with at least one moderate to severe COPD exacerbation is presented. Treated set.

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

End point timeframe:

From first in-take of study medication until 1 day after last in-take of study medication, up to 361 days

| End point values | Tiotropium 5 microgram (µg) | Tiotropium (5 µg) + Olodaterol (5 µg) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3941[7] | 3939[8] | | |
| Units: Number of patients | 1777 | 1746 | | |

Notes:

[7] - TS

[8] - TS

### Statistical analyses

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

Statistical analysis description:

A Cox's proportional hazard model was used to estimate the hazard ratio and the corresponding Confidence Interval. A log-rank test was used to obtain the p-value

| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |
|---|---|
| Number of subjects included in analysis | 7880 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[9] |
| P-value | = 0.1188 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | Other: 99 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.03 |

Notes:

[9] - This hypothesis testing strategy ensures that the overall type I error is protected at 2-sided 0.01 level. Tiotropium (5 µg) + Olodaterol (5 µg) versus Tiotropium (5 µg)
3.

### Secondary: Annualised rate of exacerbations leading to hospitalisation during the actual treatment period.

| End point title | Annualised rate of exacerbations leading to hospitalisation during the actual treatment period. |
|---|---|

End point description:

Annualised rate of exacerbations leading to hospitalisation during the actual treatment period was calculated per treatment per patient−year. The actual treatment period was defined as the interval from first in-take of study medication until 1 day after last in-take of study medication. Treated set.

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

End point timeframe:

From first in-take of study medication until 1 day after last in-take of study medication, up to 361 days

| End point values | Tiotropium 5 microgram (µg) | Tiotropium (5 µg) + Olodaterol (5 µg) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3941[10] | 3939[11] | | |
| Units: Rate per patient−year | | | | |
| least squares mean (confidence interval 95%) | 0.20 (0.18 to 0.22) | 0.18 (0.16 to 0.20) | | |

Notes:

[10] - TS

[11] - TS

### Statistical analyses

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

Statistical analysis description:

Annualised rate of exacerbations leading to hospitalization was analysed using a negative binomial model including the fixed, categorical effect of treatment as well as the logarithm of the treatment exposure as an offset.

| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |
|---|---|
| Number of subjects included in analysis | 7880 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.1265 |
| Method | Negative binomial model |
| Parameter estimate | Ratio of events vs. Tiotropium 5 µg |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.03 |

Notes:

[12] - Ratio of events Tiotropium (5 µg) + Olodaterol (5 µg) versus Tiotropium (5 µg) is provided.

### Secondary: Time to all-cause mortality occurring during the actual treatment period.

| End point title | Time to all-cause mortality occurring during the actual treatment period. |
|---|---|

End point description:

Time to all-cause mortality occurring during the actual treatment period per treatment. The actual treatment period was defined as the interval from first in-take of study medication until 1 day after last in-take of study medication. The median was not estimated due to less than 50% of patients having an event. Hence the number of patients with all-cause mortality is presented. Treated set.

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

End point timeframe:

From first in-take of study medication until 1 day after last in-take of study medication, up to 361 days

| End point values | Tiotropium 5 microgram (µg) | Tiotropium (5 µg) + Olodaterol (5 µg) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3941[13] | 3939[14] | | |
| Units: Number of patients | 32 | 36 | | |

Notes:

[13] - TS

[14] - TS

### Statistical analyses

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

Statistical analysis description:

A Cox’s proportional hazard model was used to estimate the hazard ratio and the corresponding Confidence Interval. A log-rank test was used to obtain the p-value

| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |
|---|---|
| Number of subjects included in analysis | 7880 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.7357 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.75 |

Notes:

[15] - Tiotropium (5 µg) + Olodaterol (5 µg) versus Tiotropium (5 µg)

### Secondary: Time to first COPD exacerbation leading to hospitalisation during the actual treatment period.

| End point title | Time to first COPD exacerbation leading to hospitalisation during the actual treatment period. |
|---|---|

End point description:

Time to first COPD exacerbation leading to hospitalisation during the actual treatment period per treatment. The actual treatment period was defined as the interval from first in-take of study medication until 1 day after last in-take of study medication. The median was not estimated due to less than 50% of patients having an event. Hence the number of patients with at least one moderate to severe COPD exacerbation leading to hospitalisation is presented. Treated set.

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

End point timeframe:

From first in-take of study medication until 1 day after last in-take of study medication, up to 361 days

| End point values | Tiotropium 5 microgram (µg) | Tiotropium (5 µg) + Olodaterol (5 µg) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3941[16] | 3939[17] | | |
| Units: Number of patients | 469 | 450 | | |

Notes:

[16] - TS

[17] - TS

## Statistical analyses

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

Statistical analysis description:

A Cox’s proportional hazard model was used to estimate the hazard ratio and the corresponding Confidence Interval. A log-rank test was used to obtain the p-value

| Comparison groups | Tiotropium 5 microgram (µg) v Tiotropium (5 µg) + Olodaterol (5 µg) |
|---|---|
| Number of subjects included in analysis | 7880 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[18] |
| P-value | = 0.2773 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.06 |

Notes:

[18] - Tiotropium (5 µg) + Olodaterol (5 µg) versus Tiotropium (5 µg)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of trial medication until 21 days after last in-take of trial medication, up to 381 days.

Adverse event reporting additional description:

Safety analyses were based on the treated set, which included all randomised patients who took at least 1 dose of trial medication during the randomised treatment period. Patients were only actively requested to report adverse events during the on-treatment period.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Tiotropium (5 µg) + Olodaterol (5 µg) |

Reporting group description:

Patient received 5 µg Tiotropium + 5 µg Olodaterol fixed-dose combination (FDC) inhalation solution – RESPIMAT inhaler once daily orally for 360 days.

| | |
|---|---|
| Reporting group title | Tiotropium 5 microgram (µg) |

Reporting group description:

Patient received 5 µg Tiotropium inhalation solution – RESPIMAT inhaler once daily orally for 360 days.

| Serious adverse events | Tiotropium (5 µg) + Olodaterol (5 µg) | Tiotropium 5 microgram (µg) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 810 / 3939 (20.56%) | 862 / 3941 (21.87%) | |
| number of deaths (all causes) | 92 | 98 | |
| number of deaths resulting from adverse events | 92 | 98 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basosquamous carcinoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 10 / 3939 (0.25%) | 6 / 3941 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenal neoplasm | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 5 / 3941 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder neoplasm | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer recurrent | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain neoplasm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Carcinoid tumour | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellopontine angle tumour | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cholangiocarcinoma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic myeloid leukaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer metastatic | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon neoplasm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear neoplasm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal cancer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 6 / 3939 (0.15%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic cancer | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypopharyngeal cancer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukaemia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung infiltration malignant | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 13 / 3939 (0.33%) | 7 / 3941 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm of unknown primary site | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to adrenals | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic lymphoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lymph nodes | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm prostate | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucoepidermoid carcinoma of salivary gland | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroendocrine tumour | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral haemangioma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal neoplasm | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Penis carcinoma metastatic | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary renal cell carcinoma | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal cancer | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal cancer metastatic | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic adenoma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 8 / 3939 (0.20%) | 8 / 3941 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Prostate cancer recurrent | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal adenoma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Small cell lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue neoplasm malignant stage unspecified | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsil cancer | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord neoplasm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm rupture | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic arteriosclerosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 3939 (0.08%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic thrombosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood pressure inadequately controlled | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial disorder | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 5 / 3941 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 8 / 3941 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 6 / 3939 (0.15%) | 9 / 3941 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brachiocephalic arteriosclerosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ischaemia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macroangiopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microscopic polyangiitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral embolism | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian artery occlusion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subgaleal haematoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thromboangiitis obliterans | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Enterostomy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder operation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implantable defibrillator insertion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung transplant | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic operation | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transurethral prostatectomy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 14 / 3941 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 14 | |
| deaths causally related to treatment / all | 0 / 3 | 2 / 14 | |
| Hyperplasia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 10 / 3939 (0.25%) | 11 / 3941 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated hernia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 6 / 3941 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 5 | |
| Pain | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site pain | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent restenosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Reproductive system and breast disorders** | | | |
| Acquired hydrocele | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical polyp | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst ruptured | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Alveolitis allergic | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 21 / 3939 (0.53%) | 24 / 3941 (0.61%) | |
| occurrences causally related to treatment / all | 0 / 25 | 0 / 25 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial secretion retention | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 394 / 3939 (10.00%) | 405 / 3941 (10.28%) | |
| occurrences causally related to treatment / all | 5 / 506 | 8 / 540 | |
| deaths causally related to treatment / all | 0 / 11 | 0 / 9 | |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Emphysema | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea exertional | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 3939 (0.15%) | 11 / 3941 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercapnia | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung consolidation | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiogenic pulmonary oedema | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 8 / 3941 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 3939 (0.23%) | 9 / 3941 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 11 / 3939 (0.28%) | 5 / 3941 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reflux laryngitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord polyp | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status asthmaticus | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 33 / 3939 (0.84%) | 43 / 3941 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 35 | 1 / 47 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 9 | |
| Psychiatric disorders | | | |
| Brief psychotic disorder with marked stressors | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcoholism | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol abuse | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Depression | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major depression | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Schizophrenia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panic attack | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Product issues** | | | |
| Device malfunction | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device lead damage | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device breakage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood lactic acid increased | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breath sounds absent | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test increased | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PCO2 increased | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anastomotic stenosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain herniation | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Burns second degree | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 10 / 3939 (0.25%) | 12 / 3941 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Comminuted fracture | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nail injury | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Occupational exposure to product | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial reocclusion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Petroleum distillate poisoning | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative hernia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative ileus | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Skull fracture | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress fracture | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suture rupture | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon injury | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention postoperative | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral injury | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular procedure complication | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Myocardial bridging | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Porokeratosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal anomaly congenital | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermoid cyst | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syringomyelia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Accelerated idioventricular rhythm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Aortic valve disease mixed | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 6 / 3939 (0.15%) | 14 / 3941 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute left ventricular failure | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 11 / 3939 (0.28%) | 9 / 3941 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Angina pectoris | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 8 / 3941 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 18 / 3939 (0.46%) | 12 / 3941 (0.30%) | |
| occurrences causally related to treatment / all | 1 / 20 | 2 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial flutter | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 8 / 3939 (0.20%) | 8 / 3941 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 7 | 0 / 6 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 23 / 3939 (0.58%) | 21 / 3941 (0.53%) | |
| occurrences causally related to treatment / all | 2 / 26 | 0 / 23 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 5 / 3941 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardio-respiratory arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 3939 (0.08%) | 6 / 3941 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 4 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 17 / 3939 (0.43%) | 14 / 3941 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 19 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cor pulmonale | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 5 / 3941 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cor pulmonale acute | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 8 / 3939 (0.20%) | 11 / 3941 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cor pulmonale chronic | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heart valve incompetence | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microvascular coronary artery disease | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve stenosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 10 / 3939 (0.25%) | 13 / 3941 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 6 | |
| Myocardial haemorrhage | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prinzmetal angina | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus arrest | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinoatrial block | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 3939 (0.08%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Nervous system disorders** | | | |
| Acoustic neuritis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anterior interosseous syndrome | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol induced persisting dementia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem infarction | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain injury | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral thrombosis | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 8 / 3939 (0.20%) | 7 / 3941 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | |
| Dementia | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolic cerebral infarction | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Facial paresis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial neuralgia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemianopia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Lacunar stroke | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemianaesthesia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mononeuropathy | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monoplegia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nerve root compression | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelopathy | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Quadriparesis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychomotor hyperactivity | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiculopathy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Quadriplegia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy mediastinal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Acute vestibular syndrome | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deafness | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoacusis | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden hearing loss | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Age-related macular degeneration | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amaurosis fugax | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract subcapsular | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eyelid ptosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gaze palsy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glaucoma | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Open angle glaucoma | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular fibrosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular hole | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular degeneration | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal vein thrombosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal tear | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal perforation | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erosive oesophagitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food poisoning | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated umbilical hernia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising colitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric artery thrombosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis ulcerative | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal polyp | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis chronic | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Volvulus | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stone | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis toxic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatomegaly | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swelling face | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 15 / 3939 (0.38%) | 7 / 3941 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 17 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive uropathy | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal salt-wasting syndrome | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal infarct | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral fistula | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cartilage hypertrophy | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chondrocalcinosis pyrophosphate | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 6 / 3939 (0.15%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteochondrosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sarcopenia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polymyalgia rheumatica | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tenosynovitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sjogren's syndrome | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal column stenosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Infections and infestations** | | | |
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acinetobacter infection | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Botulism | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 7 / 3941 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon gangrene | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 3939 (0.10%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Giardiasis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 4 / 3939 (0.10%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious colitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemophilus infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 10 / 3941 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 15 / 3939 (0.38%) | 15 / 3941 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 17 | 2 / 15 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Infective exacerbation of bronchiectasis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective glossitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal gangrene | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurosyphilis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral bacterial infection | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 132 / 3939 (3.35%) | 144 / 3941 (3.65%) | |
| occurrences causally related to treatment / all | 0 / 145 | 2 / 159 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 7 | |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative abscess | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoas abscess | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Scrotal abscess | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 3939 (0.23%) | 10 / 3941 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Rotavirus infection | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 5 / 3939 (0.13%) | 3 / 3941 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic arthritis staphylococcal | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Strongyloidiasis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 5 / 3941 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 12 / 3941 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte depletion | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 4 / 3941 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 2 / 3939 (0.05%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 3939 (0.00%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 2 / 3941 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3939 (0.03%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 3939 (0.08%) | 1 / 3941 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 3939 (0.03%) | 0 / 3941 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Tiotropium (5 µg) + Olodaterol (5 µg) | Tiotropium 5 microgram (µg) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1770 / 3939 (44.94%) | 1786 / 3941 (45.32%) | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 203 / 3939 (5.15%) | 232 / 3941 (5.89%) | |
| occurrences (all) | 236 | 264 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1519 / 3939 (38.56%) | 1504 / 3941 (38.16%) | |
| occurrences (all) | 2454 | 2514 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 281 / 3939 (7.13%)<br>366 | 293 / 3941 (7.43%)<br>355 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 July 2015 | The global amendment introduced administrative changes, corrections, and added clarifications. An optional spirometric assessment substudy was added. This substudy was introduced to allow for better characterisation of the air flow limitation.<br>The following exclusion criteria were revised: urinalysis was removed (exclusion criterion #2); medication restrictions and wash-out periods were updated for oral corticosteroid medication (exclusion criterion #15) and newly added for antibiotics (exclusion criterion #16). Information on permitted medications and medication restrictions as well as on restrictions on diet and life style was updated. The enrolment average per site was increased to 10 to 12 patients. The visit schedule was revised to allow the expansion of the screening period between V1 and V2 by an additional 1 week. Clarifications were introduced to the procedures for Visit 6/end of treatment, timing of procedures in case of premature discontinuation, and the Follow-up Visit. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

One site was closed for cause due to data irregularities so data of 21 patients excluded from the patient sets used for analysis. A "Missing" category is unavailable hence 1 patient with a missing age group is added to "Elderly (From 65-84 years)".

Notes: