# Clinical trial results:
# A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI) compared with the existing COPD maintenance therapy alone in subjects with Chronic Obstructive Pulmonary Disease (COPD).

## Summary

| | |
|---|---|
| EudraCT number | 2011-002452-13 |
| Trial protocol | GB |
| Global end of trial date | 24 November 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 21 September 2016 |
| First version publication date | 21 September 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | HZC115151 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | Clincial Trials Helpdesk, GlaxoSmithKline Research & Development Ltd, +44 0208990 44 66, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clincial Trials Helpdesk, GlaxoSmithKline Research & Development Ltd, +44 0208990 44 66, GSKClinicalSupportHD@gsk.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 | 23 May 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The objective of the study is to compare the effectiveness and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder 100mcg/25mcg with other maintenance therapy over twelve months in a large UK primary care population of subjects with COPD. FF/VI will be administered once-daily (QD) in the morning via the Novel Dry Powder Inhaler (NDPI).

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 March 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 3161 |
| Worldwide total number of subjects | 3161 |
| EEA total number of subjects | 3161 |

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) | 1242 |
| From 65 to 84 years | 1804 |
| 85 years and over | 115 |

## Subject disposition

### Recruitment

Recruitment details:

This was a multicenter, randomized, stratified, open-label study to evaluate the effectiveness and safety of fluticasone fuorate (FF)/vilanterol (VI) in participants (Par) followed in primary care who had a diagnosis of and received regular treatment for Chronic Obstructive Pulmonary Disease (COPD).

### Pre-assignment

Screening details:

Participants (par.) were randomized 1:1 to receive 1 inhalation of FF/VI 100 microgram (mcg)/25 mcg once daily (QD) or continued their existing maintenance therapy for 12 months. 2802 par. were randomized (3 par. randomized to the FF/VI arm did not receive study medication). A total of 2799 par. comprised the Intent to Treat (ITT) Population.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Usual Care |

Arm description:

Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Usual Care (LABA or LABA/LAMA or ICS or ICS/LABA or LABA or ICS/LABA+LAMA) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Inhaled corticosteroid alone or in combination with a long acting bronchodilator or, Long-acting bronchodilator alone or, triple maintenance therapy At appropriate dosing as instructed

| | |
|---|---|
| **Arm title** | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

Arm description:

Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FF 100 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

It is available as dry white powder containing 100 mcg of Fluticasone Furoate blended with lactose per blister and was administered by DPI, once daily in the morning.

| | |
|---|---|
| Investigational medicinal product name | VI 25 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

It is available as dry white powder containing 25 mcg of Vilanterol micronized drug (as the 'M' salt triphenylacetate) blended with lactose and magnesium stearate per blister and was administered by DPI, once daily in the morning.

| **Number of subjects in period 1[1]** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |
|---|---|---|
| Started | 1403 | 1396 |
| Completed | 1309 | 1291 |
| Not completed | 94 | 105 |
| Adverse event, serious fatal | 29 | 43 |
| Physician decision | 9 | 3 |
| Consent withdrawn by subject | 14 | 17 |
| Met Protocol-defined stopping criteria | 8 | 10 |
| Lost to follow-up | 29 | 25 |
| Protocol deviation | 5 | 6 |
| Lack of efficacy | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There were a total of 3161 participants enrolled into this study and 2799 participants were included in the ITT Population (all randomised participants who received a prescription of study medication).

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Usual Care |
| Reporting group description: | |
| Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months. | |
| Reporting group title | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |
| Reporting group description: | |
| Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally. | |

| Reporting group values | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | Total |
|---|---|---|---|
| Number of subjects | 1403 | 1396 | 2799 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 66.7 | 66.6 | |
| standard deviation | ± 9.93 | ± 9.9 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 671 | 698 | 1369 |
| Male | 732 | 698 | 1430 |
| Race<br>Units: Subjects | | | |
| African American/African Heritage | 3 | 5 | 8 |
| Asian-Central/South Asian Heritage | 5 | 6 | 11 |
| Asian-East Asian Heritage | 1 | 0 | 1 |
| Asian-South East Asian Heritage | 1 | 0 | 1 |
| White-Arabic/North African Heritage | 1 | 3 | 4 |
| White-White/Caucasian/European Heritage | 1387 | 1376 | 2763 |
| Mixed Race | 5 | 5 | 10 |
| Unknown | 0 | 1 | 1 |

## End points

### End points reporting groups

| Reporting group title | Usual Care |
|---|---|
| Reporting group description: | |
| Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months. | |
| Reporting group title | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |
| Reporting group description: | |
| Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally. | |

### Primary: Mean Annual Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

| End point title | Mean Annual Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations |
|---|---|
| End point description: | |
| Mean annual rate of moderate or severe COPD exacerbations during treatment were assessed. Moderate exacerbation: participant received exacerbation-related prescription of oral corticosteroids and/ or antibiotic (with/without National Health Service [NHS] contact) not requiring hospitalisation. Severe exacerbation: an exacerbation-related hospitalisation. Analysis method was Generalised Linear Model (GLM) assuming the negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable, adjusted for randomized treatment, baseline COPD maintenance therapy per randomisation stratification, number of moderate/severe COPD exacerbations in previous year and smoking status at baseline. Intent to treat (ITT) population: all randomised participants who received a prescription of study medication. Primary Efficacy Analysis Population: all ITT participants who had at least one moderate/severe exacerbation in the year prior to randomization. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 54 weeks | |

| End point values | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1134[1] | 1135[2] | | |
| Units: Exacerbations per participant per year | | | | |
| number (not applicable) | 1.9 | 1.74 | | |

Notes:

[1] - ITT.
This is least square mean data being entered as number due to no available dispersion measure.
[2] - ITT.
This is least square mean data being entered as number due to no available dispersion measure.

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg v Usual Care |
| Number of subjects included in analysis | 2269 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.025 |
| Method | Generalized Linear Model |
| Parameter estimate | Adjusted treatment ratio |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 0.99 |

## Secondary: Number of participants with serious adverse events (SAEs) of penumonia during the study

| End point title | Number of participants with serious adverse events (SAEs) of penumonia during the study |
|---|---|

End point description:

Incidence of SAE of pneumonia was defined for each randomized treatment group as the proportion (number) of participants in that group who experienced at least one SAE of pneumonia in the Pneumonia Adverse Event of Special Interest subgroup during the treatment period (from start date of exposure to stop date of exposure + 28 days). Non-inferiority is demonstrated if the upper limit of the two-sided 95% confidence interval for the incidence ratio is less than 2.

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

End point timeframe:

Up to 58 weeks

| End point values | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[3] | 1396[4] | | |
| Units: Participants | | | | |
| number (not applicable) | 83 | 94 | | |

Notes:

[3] - ITT Population

[4] - ITT Population

## Statistical analyses

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

Statistical analysis description:

Estimation comments: Calculated as % of participants who had at least one SAE of pneumonia in the FF/VI group divided by the % of participants who had at least one SAE of pneumonia in the Usual Care group

| | |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Incidence ratio |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.5 |

## Secondary: Mean number of serious adverse events of pnuemonia during the study

| | |
|---|---|
| End point title | Mean number of serious adverse events of pnuemonia during the study |

End point description:

The mean number of SAE of pneumonia over the treatment period (from first date of exposure to last date of exposure + 28 days was calculated. Analysis was performed using a negative binomial regression model with covariates of randomized treatment and with logarithm of time on treatment as an offset variable.

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

End point timeframe:

Up to 58 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[5] | 1396[6] | | |
| Units: Mean Number of SAE | | | | |
| number (not applicable) | 0.07 | 0.08 | | |

Notes:

[5] - ITT.
This is least square mean data being entered as number due to no available dispersion measure.
[6] - ITT.
This is least square mean data being entered as number due to no available dispersion measure.

### Statistical analyses

| **Statistical analysis title** | Statistical Ananlysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.632 |
| Method | Generalized Linear Model |
| Parameter estimate | Adjusted treatment ratio |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.47 |

## Secondary: Time to the first serious adverse event of pneumonia occuring in a year

| | |
|---|---|
| End point title | Time to the first serious adverse event of pneumonia occuring in a year |

End point description:

The analysis method was a Cox proportional hazards model adjusted for randomized treatment. Analyses included those on-treatment SAEs of pneumonia that had an onset over the first 364 days of exposure, as defined. Participants who did not have an SAE of pneumonia during the first 364 days of the treatment period (start date of exposure to end date of exposure + 28 days were considered censored.

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

End point timeframe:

Up to 52 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[7] | 1396[8] | | |
| Units: Participants | | | | |
| number (not applicable) | 80 | 89 | | |

Notes:

[7] - ITT Population

[8] - ITT Population

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.439 |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.52 |

## Secondary: Number of COPD-related secondary care contacts expressed as Least Square Mean

| | |
|---|---|
| End point title | Number of COPD-related secondary care contacts expressed as Least Square Mean |

End point description:

A COPD-related secondary care contact was defined as an inpatient admission or a specialist outpatient visit or an accident & emergency (A&E) contact. A participant with an A&E contact and subsequent inpatient admission was considered to have had two healthcare contacts. Inpatient admissions recorded at two hospitals on the same day, this was counted as a single (inpatient admission) secondary care contact. COPD-related contacts were identified using predefined lists of ICD-10 codes, specialty descriptions and diagnosis codes recorded in the patients electronic health record (EHR). GLM assuming the negative binomial distribution with log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, baseline COPD maintenance therapy per randomisation stratification, number of moderate/severe COPD exacerbations in the previous year to randomisation and smoking status at baseline.

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

End point timeframe:

Up to 54 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[9] | 1396[10] | | |
| Units: Contacts per participant per year | | | | |
| number (not applicable) | 1.48 | 1.57 | | |

Notes:

[9] - ITT.
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[10] - ITT.
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## Statistical analyses

| **Statistical analysis title** | Statistical Ananlysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.488 |
| Method | Generalized linear model |
| Parameter estimate | Adjusted treatment ratio |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.27 |

## Secondary: Number of COPD-related primary care contacts expressed using Least Square Mean

| | |
|---|---|
| End point title | Number of COPD-related primary care contacts expressed using Least Square Mean |

End point description:

A COPD-related primary care contact was defined as a primary care contact on a given calendar date with either a nurse, general physician (GP) or other healthcare professional that were considered as COPD-related, if the most prominent signs and symptoms the participant was presenting were as a direct result of the participant's COPD, as per Readcodes recorded in the patients electronic health record (EHR). The analysis method was General Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, baseline COPD maintenance therapy per randomisation stratification, number of moderate/severe COPD exacerbations in the previous year to randomisation and smoking status at baseline.

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

End point timeframe:

Up to 54 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[11] | 1396[12] | | |
| Units: Contacts per participant per year | | | | |
| number (not applicable) | 2.46 | 2.42 | | |

Notes:

[11] - ITT.
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[12] - ITT.
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## Statistical analyses

| **Statistical analysis title** | Statistical Ananlysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.622 |
| Method | Generalized Linear Model |
| Parameter estimate | Adjusted treatment ratio |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.05 |

## Secondary: Number of all secondary care contacts expressed using Least Square Mean

| | |
|---|---|
| End point title | Number of all secondary care contacts expressed using Least Square Mean |

End point description:

A secondary care contact was defined as an inpatient admission or a specialist outpatient visit or an A&E contact. A participant with an A&E contact and subsequent inpatient admission was considered to have had two healthcare contacts. In the situation where inpatient admissions were recorded at two hospitals on the same day, this was counted as a single secondary care contact. The analysis method was General Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, baseline COPD maintenance therapy per randomization stratification, number of moderate/severe COPD exacerbations in the previous year to randomization and smoking status at baseline.

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

End point timeframe:

Up to 54 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[13] | 1396[14] | | |
| Units: Contacts per participant per year | | | | |
| number (not applicable) | 9.36 | 9.81 | | |

Notes:

[13] - ITT.
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[14] - ITT.
This is least square mean data being entered as number due to no available dispersion measure.

## Statistical analyses

| **Statistical analysis title** | Statistical Ananlysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.336 |
| Method | Generalized Linear Model |
| Parameter estimate | Adjusted treatment ratio |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.15 |

## Secondary: Number of all primary care contacts expressed using Least Square Mean

| | |
|---|---|
| End point title | Number of all primary care contacts expressed using Least Square Mean |

End point description:

A primary care contact was defined as contact with a either a nurse, general practitioner, or other healthcare professional. The analysis method was General Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomized treatment, baseline COPD maintenance therapy per randomization stratification, number of moderate/severe COPD exacerbations in the previous year to randomization and smoking status at baseline.

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

End point timeframe:

Up to 54 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[15] | 1396[16] | | |
| Units: Contacts per participant per year | | | | |
| number (not applicable) | 18.88 | 21.2 | | |

Notes:

[15] - ITT.
This is least square mean data being entered as number due to no available dispersion measure.
[16] - ITT.
This is least square mean data being entered as number due to no available dispersion measure.

### Statistical analyses

| **Statistical analysis title** | Statistical Ananlysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Generalized Linear Model |
| Parameter estimate | Adjusted treatment ratio |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.05 |
| upper limit | 1.2 |

## Secondary: Time to an event of discontinuation of initial therapy occurring in a year

| | |
|---|---|
| End point title | Time to an event of discontinuation of initial therapy occurring in a year |

End point description:

Initial therapy was defined as the treatment that the subject was randomised to at randomisation. Discontinuation of initial therapy was defined as any modification of initial therapy. These included stepping up, stepping down or switching to another class/class combination, or withdrawal from the study. Switching within the same drug class did not count unless participant switched from FF/VI to a different ICS/LABA. The analysis method was a Cox proportional hazards model adjusted for randomized treatment. The probability of discontinuation of initial therapy was measured from the date of randomisation (i.e., exposure start date) to the date of discontinuation of initial therapy to which the participant was randomized, or date of treatment termination (Visit 6 or early withdrawal visit) for participants who completed the study without discontinuing the initial therapy (censored).

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

End point timeframe:

Up to 364 days

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[17] | 1396[18] | | |
| Units: Participants | | | | |
| number (not applicable) | 219 | 374 | | |

Notes:

[17] - ITT Population

[18] - ITT Population

### Statistical analyses

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

Statistical analysis description:

Estimation comments: A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual Care.

| | |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.6 |
| upper limit | 2.23 |

## Secondary: Time to the addition of a further COPD controller medication occurring in a year

| | |
|---|---|
| End point title | Time to the addition of a further COPD controller medication occurring in a year |

End point description:

The date of an event for addition of a further COPD controller medication was defined as the exposure start date of the first modified treatment medication that included a new COPD maintenance therapy of a new class of drug (to the initial therapy) during the study treatment period, as collected on the investigational product page of the eCRF. Participants who did not add any COPD controller medication during the study were censored at the end of the treatment period (Day 364). This was equivalent to stepping up, defined as the addition of at least one new class of drug. The probability of an event was measured from the date of randomization (i.e., treatment initiation) to the date of a change event. The analysis method was a Cox proportional hazards model adjusted for randomized treatment.

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

End point timeframe:

Up to 364 days

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[19] | 1396[20] | | |
| Units: Participants | | | | |
| number (not applicable) | 142 | 72 | | |

Notes:

[19] - ITT Population

[20] - ITT Population

### Statistical analyses

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

Statistical analysis description:

Estimation comments: A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual Care

| | |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Cox proprotional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 0.66 |

## Secondary: Time to first moderate/severe exacerbations occurring in a year

| | |
|---|---|
| End point title | Time to first moderate/severe exacerbations occurring in a year |

End point description:

The date of an event for moderate / severe COPD exacerbation was defined as the exacerbation onset date. The analysis method was a Cox proportional hazards model adjusted for randomized treatment. The probability of a first moderate / severe exacerbation was measured from the date of randomization (i.e., treatment initiation) to the onset date of first moderate or severe COPD exacerbation, as recorded on eCRF, or date of treatment termination (Visit 6 or early withdrawal visit) for participants who completed the study without any moderate or severe exacerbations (censored). Participants who completed the study without a moderate or severe COPD exacerbation and analyses of time to first moderate/severe exacerbation were censored at Day 364.

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

End point timeframe:

Up to 364 days

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[21] | 1396[22] | | |
| Units: Participants | | | | |
| number (not applicable) | 977 | 947 | | |

Notes:

[21] - ITT Population

[22] - ITT Population

### Statistical analyses

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

Statistical analysis description:

Estimation comments: A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual Care

| | |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.111 |
| Method | Cox porportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.02 |

## Secondary: Time to first moderate/severe exacerbations on initial therapy occurring in a year

| | |
|---|---|
| End point title | Time to first moderate/severe exacerbations on initial therapy occurring in a year |

End point description:

The date of an event for moderate / severe COPD exacerbation was defined as the exacerbation onset date. The analysis method was a Cox proportional hazards model adjusted for randomized treatment. The probability of first moderate / severe exacerbation on initial therapy was measured from the date of randomization (i.e., exposure start date) to the onset date of first moderate or severe COPD exacerbation, or to the date of discontinuation of initial therapy (analysis was censored at date of discontinuation of initial therapy) for participants who completed the study without any moderate or severe exacerbations on initial therapy.

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

End point timeframe:

Up to 364 days

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[23] | 1396[24] | | |
| Units: Participants | | | | |
| number (not applicable) | 943 | 852 | | |

Notes:

[23] - ITT Population

[24] - ITT Population

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.081 |
| Method | Cox porportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.01 |

## Secondary: Time to first severe exacerbations occurring in a year

| | |
|---|---|
| End point title | Time to first severe exacerbations occurring in a year |

End point description:

The date of an event for severe exacerbation was defined as the exacerbation onset date. Participants who completed the study without a severe exacerbation were censored. The analysis method was a Cox proportional hazards model adjusted for randomized treatment.
The probability of first severe exacerbation was measured from the date of randomization (i.e., treatment initiation) to the onset date of first severe exacerbation, as recorded on eCRF, or date of treatment termination (Visit 6 or early withdrawal visit) for participants who completed the study without any severe exacerbations (censored). At Day 364, all participants who have not experienced a severe exacerbation are considered censored, regardless of whether their on-treatment phase continues beyond day 364, including those who withdrew early.

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

End point timeframe:

Up to 364 days

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[25] | 1396[26] | | |
| Units: Participants | | | | |
| number (not applicable) | 97 | 122 | | |

Notes:

[25] - ITT Population

[26] - ITT Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 2799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.075 |
| Method | Cox porportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.66 |

## Secondary: Number of participants with Fatal serious adverse events of pneumonia

| | |
|---|---|
| End point title | Number of participants with Fatal serious adverse events of pneumonia |

End point description:

All SAEs included in the AE subgroup of special interest of "pneumonia" were considered as an SAE of pneumonias. A fatal SAE was defined as a SAE with outcome of fatal for study participant. The number of participants with fatal SAEs of pneumonia was assessed over 14 months.

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

End point timeframe:

Up to 58 weeks

| End point values | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[27] | 1396[28] | | |
| Units: Participants | | | | |
| number (not applicable) | 13 | 13 | | |

Notes:

[27] - ITT Population

[28] - ITT Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with non-serious adverse drug reactions (ADR)

| | |
|---|---|
| End point title | Number of participants with non-serious adverse drug reactions (ADR) |

End point description:

The number of participants with non-serious ADRs was assessed for up to 54 weeks. An ADR is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is causally related to the medicinal product. A non-serious ADR included one of the following: exacerbation of chronic or intermittent pre-existing condition; signs, symptoms, or the clinical sequelae of a

suspected interaction; signs, symptoms, or new conditions detected or diagnosed after study treatment administration.

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

End point timeframe:

Up to 54 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[29] | 1396[30] | | |
| Units: Participants | | | | |
| number (not applicable) | 88 | 192 | | |

Notes:

[29] - ITT Population

[30] - ITT Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with serious adverse events

| End point title | Number of participants with serious adverse events |
|---|---|

End point description:

SAEs assessed included medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a significant medical event in the investigator's judgment, or is an event of possible drug-induced liver injury with hyperbilirubinemia. SAEs were includes if the onset date was on or after the treatment start date and on or before the treatment stop date. However, the window for an SAE of pneumonia was longer and included 28 days post study treatment stop date.

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

End point timeframe:

Up to 56 weeks

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[31] | 1396[32] | | |
| Units: Participants | | | | |
| number (not applicable) | 383 | 404 | | |

Notes:

[31] - ITT Population

[32] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with serious adverse drug reactions

| End point title | Number of participants with serious adverse drug reactions |
|---|---|

End point description:

A serious adverse drug reactions (SADR) is any untoward medical occurrence suspected to be medicinal product-related that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

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

End point timeframe:

Upto 12 months

| **End point values** | Usual Care | Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1403[33] | 1396[34] | | |
| Units: Participants | | | | |
| number (not applicable) | 10 | 23 | | |

Notes:

[33] - ITT Population

[34] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs; from Visit 1) and non-serious AE and adverse drug reactions (from Visit 2) were collected from study medication start until the end of treatment (up to Visit 6 or withdrawal, i.e, approximately 54 weeks)

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Usual Care |

Reporting group description:

Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months

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

Reporting group description:

Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally.

| Serious adverse events | Usual Care | FF/VI 100 mcg/25 mcg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 383 / 1403 (27.30%) | 404 / 1396 (28.94%) | |
| number of deaths (all causes) | 50 | 77 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bladder neoplasm | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowen’s disease | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain neoplasm | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carcinoma in situ of skin | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid body tumour | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic lymphocytic leukaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic lymphocytic leukaemia recurrent | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon neoplasm | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal carcinoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal tract adenoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glioblastoma multiforme | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Glottis carcinoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cancer metastatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic neoplasm | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung carcinoma cell type unspecified recurrent | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 7 / 1403 (0.50%) | 10 / 1396 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 5 | |
| Lung squamous cell carcinoma recurrent | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung squamous cell carcinoma stage 0 | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung squamous cell carcinoma stage IV | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mantle cell lymphoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 | 3 / 1403 (0.21%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Metastases to lung | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lymph nodes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer recurrent | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic adenoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Refractory anaemia with an excess of blasts | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of Lung | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ureteral neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric cancer | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular disorders | | | |
| Angiodysplasia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aortic aneurysm rupture | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aortic thrombosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure inadequately controlled | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 9 / 1396 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral artery occlusion | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Surgical and medical procedures** | | | |
| Carotid endarterectomy | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hospitalisation | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **General disorders and administration site conditions** | | | |
| Chest pain | | | |
| subjects affected / exposed | 8 / 1403 (0.57%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cyst | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Hypothermia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stent-graft endoleak | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Unintentional medical device removal | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent occlusion | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Allergic granulomatous angiitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Drug hypersensitivity | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial secretion retention | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 4 / 1403 (0.29%) | 6 / 1396 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 70 / 1403 (4.99%) | 86 / 1396 (6.16%) | |
| occurrences causally related to treatment / all | 1 / 82 | 4 / 94 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 5 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pickwickian syndrome | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural fibrosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 8 / 1396 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 3 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 24 / 1403 (1.71%) | 15 / 1396 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 28 | 0 / 18 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sputum retention | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stridor | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium tremens | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major depression | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Self-injurious ideation | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood electrolytes abnormal | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 6 / 1403 (0.43%) | 15 / 1396 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic specific antigen increased | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal function test abnormal | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 12 / 1396 (0.86%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol poisoning | | | |

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|---|---|---|---|
| subjects affected / exposed | 4 / 1403 (0.29%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 5 / 1403 (0.36%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brachial plexus injury | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac valve rupture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chemical injury | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest injury | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contrast media reaction | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Craniocerebral injury | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 15 / 1396 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Forearm fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foreign body aspiration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 4 / 1403 (0.29%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 8 / 1396 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intentional overdose | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Open fracture | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax traumatic | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation mucositis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 | 5 / 1403 (0.36%) | 8 / 1396 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic rupture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Stress fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| 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 | 3 / 1403 (0.21%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral injury | | | |

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| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Phimosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 12 / 1403 (0.86%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 13 / 1396 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Angina pectoris | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 4 / 1403 (0.29%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 29 / 1403 (2.07%) | 27 / 1396 (1.93%) | |
| occurrences causally related to treatment / all | 1 / 33 | 2 / 28 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradyarrhythmia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 11 / 1403 (0.78%) | 10 / 1396 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 5 / 1403 (0.36%) | 6 / 1396 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cor pulmonale | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 4 / 1403 (0.29%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 6 / 1396 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Palpitations | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| 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 | 0 / 1403 (0.00%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trifascicular block | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Basal ganglia infarction | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain injury | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Brain mass | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery aneurysm | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery disease | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid sinus syndrome | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 5 / 1403 (0.36%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cervical myelopathy | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia with Lewy bodies | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| 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 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug withdrawal convulsions | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 6 / 1403 (0.43%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningism | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiculitis brachial | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sedation | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 4 / 1403 (0.29%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 10 / 1403 (0.71%) | 11 / 1396 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 10 | 1 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 11 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Unresponsive to stimuli | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIIth nerve paralysis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular dementia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord paresis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 1403 (0.43%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Coagulopathy | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microcytic anaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 4 / 1403 (0.29%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Normochromic normocytic anaemia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pernicious anaemia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Blindness unilateral | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 1403 (0.29%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Barrett’s oesophagus | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coeliac disease | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 1403 (0.36%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer perforation | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyskinesia oesophageal | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric dysplasia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 / 1403 (0.14%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal spasm | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic insufficiency | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Alcoholic liver disease | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder perforation | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Skin and subcutaneous tissue disorders** | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Miliaria | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 | 16 / 1403 (1.14%) | 23 / 1396 (1.65%) | |
| occurrences causally related to treatment / all | 0 / 19 | 1 / 24 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| 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 | 5 / 1403 (0.36%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal artery stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal disorder | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 7 / 1403 (0.50%) | 10 / 1396 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal mass | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sterile pyuria | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 7 / 1403 (0.50%) | 8 / 1396 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperparathyroidism primary | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthyroidism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inappropriate antidiuretic ormone secretion | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 | 3 / 1403 (0.21%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle necrosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| 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 | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 6 / 1403 (0.43%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue swelling | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 sepsis | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess oral | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspergillus infection | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical mycobacterial infection | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary sepsis | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bronchitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 9 / 1403 (0.64%) | 14 / 1396 (1.00%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endophthalmitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 4 / 1403 (0.29%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma infection | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster meningoencephalitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of bronchiectasis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 47 / 1403 (3.35%) | 50 / 1396 (3.58%) | |
| occurrences causally related to treatment / all | 0 / 56 | 1 / 57 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| 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 | 10 / 1403 (0.71%) | 12 / 1396 (0.86%) | |
| occurrences causally related to treatment / all | 1 / 10 | 2 / 12 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphangitis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mycetoma mycotic | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 3 / 1403 (0.21%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic abscess | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 81 / 1403 (5.77%) | 89 / 1396 (6.38%) | |
| occurrences causally related to treatment / all | 4 / 94 | 3 / 98 | |
| deaths causally related to treatment / all | 1 / 13 | 0 / 12 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| 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 / 1403 (0.07%) | 0 / 1396 (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 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

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|---|---|---|---|
| subjects affected / exposed | 10 / 1403 (0.71%) | 9 / 1396 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Septic embolus | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 1403 (0.86%) | 9 / 1396 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella zoster virus infection | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral labyrinthitis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 6 / 1396 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 6 / 1403 (0.43%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemochromatosis | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 4 / 1396 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperosmolar hyperglycaemic state | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 1403 (0.14%) | 2 / 1396 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 1403 (0.14%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 7 / 1403 (0.50%) | 7 / 1396 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 1403 (0.07%) | 0 / 1396 (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 | 3 / 1403 (0.21%) | 5 / 1396 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obesity | | | |
| subjects affected / exposed | 0 / 1403 (0.00%) | 1 / 1396 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 5 / 1403 (0.36%) | 3 / 1396 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Usual Care | FF/VI 100 mcg/25 mcg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 1403 (2.85%) | 56 / 1396 (4.01%) | |
| Infections and infestations | | | |
| Oral candidiasis | Additional description: In this study, only information regarding non- serious adverse drug reactions (ADRs) and serious adverse events (SAEs) were detected, documented and reported. | | |
| subjects affected / exposed | 40 / 1403 (2.85%) | 56 / 1396 (4.01%) | |
| occurrences (all) | 42 | 57 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 July 2013 | Study design was amended: total # of par. required for study; changes (chg) to the Time Interval (int) for Visit 1; clarified the definition of a moderate exacerbation and NHS contacts in relation to the primary endpoint; clarified the secondary endpoint as COPD related rather than respiratory; added the # of actuations in salbutamol inhalers; added changes in relation to childbearing potential and to exclusion criteria 3 in relation to par. with unstable COPD; added chg in relation to ECG QTc prolongation; included the requirement (req) for signed consent form in definition of screen failure; added short-acting-beta2 agonist as generic class; added a statement (stat) on Adherence as Medication (med.) Possession Ratio; added a stat that all concomitant med. used in the study were to be recorded; removed the list of permitted COPD med. and added stat that all COPD med. were permitted with exceptions listed in Section 4.9.2; added new paragraphs in the section on Prohibited Med. and Non-Drug Therapies; amended the Time &Events Table to include chg in the Visit 1 time interval; genetic sampling and height and weight in the demographic information; added a new section Baseline Cardiovascular Co-Morbid Conditions and Severe Pneumonia History; added definition of History of Pneumonia; state that par. unable to perform spirometry would not be excluded; added the FF/VI in Section 5.3.1 to replace study drug or investigational drug; added a new Section 5.1.4 titled Research data not required for eCRF (crude EHR data); added a new genetics section Amend Section 7.2.1 on Sample Size Assumption to take into account reduced # of par.; added a new reference in relation to GOLD in the Primary Objectives; amended the Study Schematic in relation to the time interval at Visit 1 from Day -30 to Day -60; added a new Appendix 10.4 Genetic section; added a new Appendix 10.5 which identifies all the changes to the protocol; and minor formatting changes. |
| 21 August 2013 | Removed Section 5.1.1; History of serious pneumonia, defined as the total number of episodes with a pneumonia diagnosis for the hospitalization, in the 12 months prior to randomization were identified based on the EHR and recorded in the eCRF; added to Section5.1.4: History of serious pneumonia, defined as the total number of episodes with a pneumonia diagnosis for the hospitalization, in the 3 years prior to randomization were identified based on the EHR. In Section 4.4.1, the following text 'used due to SAE' was deleted. |
| 30 September 2013 | All references to 'this protocol amendment' changed to 'protocol amendment 1'; all references to Salford, Greater Manchester expanded to Salford and South Manchester, Greater Manchester, to reflect the increase in regional sites. Reference to eligible population in Salford removed as catchment area is now beyond Salford; NHS contacts text changed to include healthcare professionals; withdrawal of FF/VI reference clarified to show they can continue in the study on a maintenance therapy. Reference to study medication clarified to indicate FF/VI medication; reference to concomitant medications used clarified to reflect concomitant medication prescribed and dispensed; reference to collection of pharmacy data 'drug trade name' changed to 'drug name'. Table 2 corrected to remove incorrectly shaded cells. Crude EHR data amended to add additional secondary care site, University Hospital South Manchester. Genetics research; erroneous references added in error and text modified to reflect current standard text. |
| 09 December 2013 | Updated author list; Secondary objectives and safety endpoints updated to include pneumonia SAEs and analysis. Addition of pharmacy EHR as source of dispensing data and exclusion criteria to exclude 8. Subjects whose current medications include RELVAR™, ELLIPTA™ are not eligible to enter the study. If patients change to RELVAR™, ELLIPTA™ as their maintenance therapy, they should be withdrawn from the study. Data Analysis and Statistical Considerations updated to reflect the additional endpoint for pneumonia SAEs; References added. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported