# Clinical trial results:
# A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 compared to PT005 on COPD Exacerbations over a variable-length (12-52 week) Treatment Period in Subjects With Moderate to Very Severe COPD

## Summary

| | |
|---|---|
| EudraCT number | 2016-000155-28 |
| Trial protocol | DK BE GB DE ES AT IT |
| Global end of trial date | 04 April 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 April 2019 |
| First version publication date | 21 April 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | PT009003 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02727660 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Pearl Therapeutics, a Member of the AstraZeneca Group |
| Sponsor organisation address | 200 Cardinal Way, Redwood City, United States, 94063 |
| Public contact | Paul M. Dorinsky, MD, Pearl Therapeutics, a Member of the AstraZeneca Group, 1 6503052600, paul.dorinsky1@astrazeneca.com |
| Scientific contact | Paul M. Dorinsky, MD, Pearl Therapeutics, a Member of the AstraZeneca Group, 1 6503052600, paul.dorinsky1@astrazeneca.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 | 04 April 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 April 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 April 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the effects of BFF MDI relative to FF MDI on lung function.

Protection of trial subjects:

Subjects who are receiving an ICS/LABA will discontinue the ICS/LABA, but continue the ICS component for the remainder of the Screening Period.
Subjects treated with an ICS as part of their inhaled maintenance therapy will continue their ICS for the remainder of the Screening Period.
Sponsor-provided Ventolin HFA to be administered as needed, up to 8 inhalations per day, for control of COPD symptoms.
Subjects receiving phosphodiesterase inhibitors (e.g., roflumilast) at stable doses for at least 4 weeks prior to Visit 1, may continue on these medications throughout the Screening and Randomized Treatment periods.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 29 April 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 182 |
| Country: Number of subjects enrolled | Austria: 22 |
| Country: Number of subjects enrolled | Belgium: 24 |
| Country: Number of subjects enrolled | Brazil: 62 |
| Country: Number of subjects enrolled | Canada: 34 |
| Country: Number of subjects enrolled | Chile: 41 |
| Country: Number of subjects enrolled | Germany: 49 |
| Country: Number of subjects enrolled | Denmark: 65 |
| Country: Number of subjects enrolled | Spain: 61 |
| Country: Number of subjects enrolled | United Kingdom: 24 |
| Country: Number of subjects enrolled | Italy: 37 |
| Country: Number of subjects enrolled | Mexico: 74 |
| Country: Number of subjects enrolled | Norway: 29 |
| Country: Number of subjects enrolled | Peru: 132 |
| Country: Number of subjects enrolled | Russian Federation: 123 |
| Country: Number of subjects enrolled | Sweden: 23 |

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 761 |
| Country: Number of subjects enrolled | South Africa: 100 |
| Worldwide total number of subjects | 1843 |
| EEA total number of subjects | 334 |

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) | 844 |
| From 65 to 84 years | 999 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study screened subjects at 292 study centers  in 18 countries and randomized subjects at 259 study centers, from May 2016 to April 2018.

### Pre-assignment

Screening details:

Subjects were randomized in a 1:1:1 ratio to BFF MDI 320/9.6 µg, BFF MDI 160/9.6 µg, and FF MDI 9.6 µg treatment groups

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | BFF MDI 320/9.6 ug |

Arm description:

Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Budesonide Formoterol Fumarate MDI |
| Investigational medicinal product code | |
| Other name | BFF MDI 160/4.8 ug |
| Pharmaceutical forms | Pressurised inhalation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

Taken as 2 inhalations BID

| | |
|---|---|
| **Arm title** | BFF MDI 160/9.6 ug |

Arm description:

Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Budesonide Formoterol Fumarate MDI |
| Investigational medicinal product code | |
| Other name | BFF MDI 80/4.8 ug |
| Pharmaceutical forms | Pressurised inhalation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

Taken as 2 inhalations BID

| | |
|---|---|
| **Arm title** | FF MDI 9.6 ug |

Arm description:

Formoterol Fumarate Metered dose inhalation 9.6 ug

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Formoterol Fumarate MDI |
| Investigational medicinal product code | |
| Other name | FF MDI 4.8 ug |
| Pharmaceutical forms | Pressurised inhalation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

Taken as 2 inhalations BID

| **Number of subjects in period 1** | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug |
|---|---|---|---|
| Started | 619 | 617 | 607 |
| Completed | 503 | 501 | 442 |
| Not completed | 116 | 116 | 165 |
| Administrative Reasons | 2 | 3 | 4 |
| Consent withdrawn by subject | 26 | 25 | 30 |
| Physician decision | 3 | 8 | 14 |
| Adverse event, non-fatal | 28 | 21 | 32 |
| Protocol Specified Disc. Criteria | 5 | 5 | 2 |
| Lost to follow-up | 5 | 9 | 8 |
| Lack of efficacy | 40 | 40 | 70 |
| Protocol deviation | 7 | 5 | 5 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | BFF MDI 320/9.6 ug |
| Reporting group description: | |
| Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug | |
| Reporting group title | BFF MDI 160/9.6 ug |
| Reporting group description: | |
| Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug | |
| Reporting group title | FF MDI 9.6 ug |
| Reporting group description: | |
| Formoterol Fumarate Metered dose inhalation 9.6 ug | |

| Reporting group values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug |
|---|---|---|---|
| Number of subjects | 619 | 617 | 607 |
| Age categorical | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 272 | 299 | 273 |
| From 65-84 years | 347 | 318 | 334 |
| Age Continuous | | | |
| mITT Population | | | |
| Units: years | | | |
| arithmetic mean | 65.3 | 64.5 | 64.8 |
| standard deviation | ± 8.1 | ± 8.4 | ± 8.5 |
| Sex: Female, Male | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Female | 252 | 272 | 268 |
| Male | 367 | 345 | 339 |
| Race (NIH/OMB) | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 26 | 18 | 24 |
| Asian | 1 | 7 | 4 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 |
| Black or African American | 30 | 22 | 29 |
| White | 514 | 516 | 504 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 47 | 54 | 46 |
| Ethnicity (NIH/OMB) | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 190 | 200 | 190 |
| Not Hispanic or Latino | 423 | 414 | 412 |
| Unknown or Not Reported | 6 | 3 | 5 |

| Reporting group values | Total | | |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Number of subjects | 1843 | | |
| Age categorical | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 844 | | |
| From 65-84 years | 999 | | |
| Age Continuous | | | |
| mITT Population | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Female | 792 | | |
| Male | 1051 | | |
| Race (NIH/OMB) | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 68 | | |
| Asian | 12 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| Black or African American | 81 | | |
| White | 1534 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 147 | | |
| Ethnicity (NIH/OMB) | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 580 | | |
| Not Hispanic or Latino | 1249 | | |
| Unknown or Not Reported | 14 | | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | mITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The Modified Intent-To-Treat (mITT) Population is defined as all subjects who were randomized to treatment, received any amount of the study treatment, and had post-randomization data obtained prior to discontinuation from treatment.

| | |
|---|---|
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety Population is defined as all subjects who were randomized to treatment and received at least one dose of the study treatment. Subjects are analyzed according to treatment received rather than randomized.

| **Reporting group values** | mITT | Safety Population | |
|---|---|---|---|
| Number of subjects | 1843 | 1843 | |

| | | | |
|---|---|---|---|
| Age categorical | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 844 | 844 | |
| From 65-84 years | 999 | 999 | |
| Age Continuous | | | |
| mITT Population | | | |
| Units: years | | | |
| arithmetic mean | 64.9 | 64.9 | |
| standard deviation | ± 8.3 | ± 8.3 | |
| Sex: Female, Male | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Female | 792 | 792 | |
| Male | 1051 | 1051 | |
| Race (NIH/OMB) | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 68 | 68 | |
| Asian | 12 | 12 | |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | |
| Black or African American | 81 | 81 | |
| White | 1534 | 1534 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 147 | 147 | |
| Ethnicity (NIH/OMB) | | | |
| mITT Population | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 580 | 580 | |
| Not Hispanic or Latino | 1249 | 1249 | |
| Unknown or Not Reported | 14 | 14 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | BFF MDI 320/9.6 ug |
| Reporting group description: | |
| Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug | |
| Reporting group title | BFF MDI 160/9.6 ug |
| Reporting group description: | |
| Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug | |
| Reporting group title | FF MDI 9.6 ug |
| Reporting group description: | |
| Formoterol Fumarate Metered dose inhalation 9.6 ug | |
| Subject analysis set title | mITT |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| The Modified Intent-To-Treat (mITT) Population is defined as all subjects who were randomized to treatment, received any amount of the study treatment, and had post-randomization data obtained prior to discontinuation from treatment. | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety Population is defined as all subjects who were randomized to treatment and received at least one dose of the study treatment. Subjects are analyzed according to treatment received rather than randomized. | |

### Primary: Morning pre-dose trough FEV1

| | |
|---|---|
| End point title | Morning pre-dose trough FEV1 |
| End point description: | |
| Morning pre-dose trough FEV1 (Forced Expiratory Volume in one second) over 24 weeks | |
| End point type | Primary |
| End point timeframe: | |
| over 24 weeks | |

| End point values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 578 | 590 | 559 | |
| Units: Liter | | | | |
| least squares mean (confidence interval 95%) | 0.063 (0.047 to 0.079) | 0.059 (0.044 to 0.074) | 0.024 (0.009 to 0.040) | |

### Statistical analyses

| Statistical analysis title | Morning pre-dose trough FEV1 |
|---|---|
| Statistical analysis description: | |
| Primary endpoint analysis - BFF MDI versus FF MDI | |
| Comparison groups | BFF MDI 320/9.6 ug v FF MDI 9.6 ug |

| | |
|---|---|
| Number of subjects included in analysis | 1137 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≥ 0.05 |
| Method | repeated measures linear mixed model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.018 |
| upper limit | 0.059 |

| **Statistical analysis title** | Morning pre-dose trough FEV1 |
|---|---|
| Statistical analysis description: | |
| Primary endpoint analysis - BFF MDI versus FF MDI | |
| Comparison groups | BFF MDI 160/9.6 ug v FF MDI 9.6 ug |
| Number of subjects included in analysis | 1149 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≥ 0.05 |
| Method | repeated measures linear mixed model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.05 |
| Confidence interval | |
| level | Other: 0.03 % |
| sides | 2-sided |
| lower limit | 0.014 |
| upper limit | 0.055 |

| **Secondary: Time to first moderate or severe COPD exacerbation** | |
|---|---|
| End point title | Time to first moderate or severe COPD exacerbation |
| End point description: | |
| Time to first moderate or severe COPD (Chronic Obstructive Pulmonary Disease) exacerbation over 52 weeks | |
| End point type | Secondary |
| End point timeframe: | |
| over 52 weeks | |

| End point values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 619 | 617 | 607 | |
| Units: Participants | | | | |
| No of subj with ≥1 events | 220 | 223 | 241 | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to first clinically important deterioration in COPD

| End point title | Time to first clinically important deterioration in COPD |
|---|---|

End point description:

Time to first clinically important deterioration in COPD over 52 weeks

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

End point timeframe:

over 52 weeks

| End point values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 619 | 617 | 607 | |
| Units: Number | 469 | 462 | 491 | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in average daily rescue Ventolin HFA use

| End point title | Change from baseline in average daily rescue Ventolin HFA use |
|---|---|

End point description:

Change from baseline in average daily rescue Ventolin HFA use over 24 weeks

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

End point timeframe:

over 24 weeks

| End point values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 612 | 610 | 599 | |
| Units: Puffs per day | | | | |
| least squares mean (confidence interval 95%) | -1.0 (-1.2 to -0.8) | -1.0 (-1.1 to -0.8) | -0.6 (-0.8 to -0.4) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of subjects achieving an MCID (Minimal clinically important difference) of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score

| End point title | Percentage of subjects achieving an MCID (Minimal clinically important difference) of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score |
|---|---|

End point description:

Percentage of subjects achieving an MCID (Minimal clinically important difference) of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score over 24 weeks

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

End point timeframe:

over 24 weeks

| End point values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 606[1] | 613[2] | 596[3] | |
| Units: scores on a scale | | | | |
| Percent observed | 53 | 53 | 43 | |

Notes:

[1] - Observed % (n/N) for Treatment 320/606

[2] - Observed % (n/N) for Treatment 326/613

[3] - Observed % (n/N) for Treatment 254/596

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period

| End point title | Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period |
|---|---|

End point description:

Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period over 52 weeks

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

End point timeframe:
over 52 weeks

| End point values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 614 | 613 | 597 | |
| Units: scores on a scale | | | | |
| least squares mean (confidence interval 95%) | -2.4 (-3.2 to -1.6) | -2.5 (-3.3 to -1.7) | -1.0 (-1.8 to -0.2) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Transient Dyspnea Index (TDI) focal score

| End point title | Transient Dyspnea Index (TDI) focal score |
|---|---|

End point description:
Transient Dyspnea Index (TDI) focal score over 24 weeks

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

End point timeframe:
over 24 weeks

| End point values | BFF MDI 320/9.6 ug | BFF MDI 160/9.6 ug | FF MDI 9.6 ug | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 566 | 578 | 550 | |
| Units: scores on a scale | | | | |
| least squares mean (confidence interval 95%) | 1.32 (1.10 to 1.53) | 1.30 (1.09 to 1.51) | 1.06 (0.85 to 1.28) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time the subject signed informed consent throughout the treatment period and up to 14 days following the last dose of study drug.

Adverse event reporting additional description:

Serious Adverse Events were collected from the time the subject signed informed consent throughout the treatment period and up to approximately 52 weeks, which includes screening and follow up (14 days after last dose of study drug).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | BFF MDI 320/9.6 ug |

Reporting group description:

Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug

| | |
|---|---|
| Reporting group title | FF MDI 9.6 ug |

Reporting group description:

Formoterol Fumarate Metered dose inhalation 9.6 ug

| | |
|---|---|
| Reporting group title | BFF MDI 160/9.6 ug |

Reporting group description:

Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug

| Serious adverse events | BFF MDI 320/9.6 ug | FF MDI 9.6 ug | BFF MDI 160/9.6 ug |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 60 / 619 (9.69%) | 83 / 607 (13.67%) | 78 / 617 (12.64%) |
| number of deaths (all causes) | 3 | 8 | 4 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 2 / 619 (0.32%) | 1 / 607 (0.16%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma stage III | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic Cancer | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma stage III | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung cancer metastatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mantle cell lymphoma | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral vascular disease | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 619 (0.32%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 27 / 619 (4.36%) | 50 / 607 (8.24%) | 30 / 617 (4.86%) |
| occurrences causally related to treatment / all | 0 / 32 | 0 / 65 | 0 / 33 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 2 / 619 (0.32%) | 6 / 607 (0.99%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 1 / 607 (0.16%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercapnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary alveolar haemorrhage | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status change | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 1 / 607 (0.16%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alcohol withdrawal syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal injury | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Fascial rupture | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 4 / 607 (0.66%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 619 (0.16%) | 1 / 607 (0.16%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrilation | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 3 / 617 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 2 / 607 (0.33%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cor pulmonae | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Nervous system disorders** | | | |
| Brain injury | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic neuropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular encephalopathy | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 2 / 607 (0.33%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 2 / 607 (0.33%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 3 / 617 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal hernia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peptic ulcer | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 2 / 607 (0.33%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal tubular acidosis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric obstruction | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 619 (0.97%) | 9 / 607 (1.48%) | 12 / 617 (1.94%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 9 | 0 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 1 / 607 (0.16%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 619 (0.16%) | 2 / 607 (0.33%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 2 / 617 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridial infection | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocele male infected | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pnuemonia mycoplasmal | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 619 (0.00%) | 0 / 607 (0.00%) | 1 / 617 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 619 (0.16%) | 0 / 607 (0.00%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovalaemia | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type II diabetes mellitus | | | |
| subjects affected / exposed | 0 / 619 (0.00%) | 1 / 607 (0.16%) | 0 / 617 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| **Non-serious adverse events** | BFF MDI 320/9.6 ug | FF MDI 9.6 ug | BFF MDI 160/9.6 ug |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 266 / 619 (42.97%) | 268 / 607 (44.15%) | 279 / 617 (45.22%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 15 / 619 (2.42%) | 14 / 607 (2.31%) | 15 / 617 (2.43%) |
| occurrences (all) | 15 | 14 | 15 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 16 / 619 (2.58%) | 18 / 607 (2.97%) | 19 / 617 (3.08%) |
| occurrences (all) | 24 | 20 | 24 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 619 (2.10%) | 10 / 607 (1.65%) | 10 / 617 (1.62%) |
| occurrences (all) | 14 | 11 | 11 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 27 / 619 (4.36%) | 50 / 607 (8.24%) | 30 / 617 (4.86%) |
| occurrences (all) | 32 | 65 | 33 |
| Dyspnoea | | | |
| subjects affected / exposed | 23 / 619 (3.72%) | 16 / 607 (2.64%) | 16 / 617 (2.59%) |
| occurrences (all) | 23 | 18 | 19 |
| Cough | | | |
| subjects affected / exposed | 14 / 619 (2.26%) | 9 / 607 (1.48%) | 15 / 617 (2.43%) |
| occurrences (all) | 15 | 9 | 17 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 15 / 619 (2.42%) | 11 / 607 (1.81%) | 17 / 617 (2.76%) |
| occurrences (all) | 21 | 13 | 17 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 41 / 619 (6.62%) | 36 / 607 (5.93%) | 53 / 617 (8.59%) |
| occurrences (all) | 53 | 43 | 61 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 28 / 619 (4.52%) | 24 / 607 (3.95%) | 14 / 617 (2.27%) |
| occurrences (all) | 29 | 28 | 18 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 619 (2.26%) | 15 / 607 (2.47%) | 19 / 617 (3.08%) |
| occurrences (all) | 14 | 15 | 20 |
| Influenza | | | |
| subjects affected / exposed | 15 / 619 (2.42%) | 10 / 607 (1.65%) | 19 / 617 (3.08%) |
| occurrences (all) | 15 | 10 | 20 |
| Bronchitis | | | |
| subjects affected / exposed | 11 / 619 (1.78%) | 10 / 607 (1.65%) | 13 / 617 (2.11%) |
| occurrences (all) | 11 | 14 | 15 |
| Sinusitis | | | |
| subjects affected / exposed | 9 / 619 (1.45%) | 13 / 607 (2.14%) | 9 / 617 (1.46%) |
| occurrences (all) | 9 | 13 | 11 |
| Acute sinusitis | | | |
| subjects affected / exposed | 2 / 619 (0.32%) | 12 / 607 (1.98%) | 6 / 617 (0.97%) |
| occurrences (all) | 2 | 17 | 10 |
| Oral candidiasis | | | |
| subjects affected / exposed | 13 / 619 (2.10%) | 7 / 607 (1.15%) | 6 / 617 (0.97%) |
| occurrences (all) | 16 | 8 | 7 |
| Urinary tract infection | | | |
| subjects affected / exposed | 10 / 619 (1.62%) | 13 / 607 (2.14%) | 18 / 617 (2.92%) |
| occurrences (all) | 12 | 15 | 20 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 July 2016 | Sponsor contact information updated, Clarification to study population, updated inclusion/exclusion criteria, con meds, allowed meds, prohibited meds, and visit schedule. |
| 15 December 2016 | Updated study objectives, study design and plan, study duration, exacerbation history, and procedures. |
| 08 January 2018 | Clarified synopsis, HCRU endpoints, smoking status, estimands, mITT population. Updated statistical model definition of CID across PT010 & PT009 programs. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported