



Clinical trial results:

A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-004712-10 |
| Trial protocol | DE CZ PL HU |
| Global end of trial date | 31 August 2017 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 07 September 2018 |
| First version publication date | 07 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | PT003014 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02343458 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pearl Therapeutics Inc. |
| Sponsor organisation address | 200 Cardinal Way, Redwood City, United States, 94063 |
| Public contact | Colin Reisner, Pearl Therapeutics Inc., 1 6503052600, creisner@pearltherapeutics.com |
| Scientific contact | Colin Reisner, Pearl Therapeutics Inc., 1 6503052600, creisner@pearltherapeutics.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 | 31 August 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 August 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to Placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough forced expiratory volume in 1 second (FEV1) in subjects with moderate to very severe COPD.

Protection of trial subjects:

For subjects who were on ICS LABA, the ICS LABA was discontinued, however, then prescribed an ICS Monotherapy at an equivalent dosing regimen for the duration of the study.

Subjects were also given sponsor provided Ventolin HFA as rescue medication.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 30 March 2015 |
| 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 | China: 466 |
| Country: Number of subjects enrolled | Czech Republic: 48 |
| Country: Number of subjects enrolled | Germany: 126 |
| Country: Number of subjects enrolled | United Kingdom: 56 |
| Country: Number of subjects enrolled | Hungary: 82 |
| Country: Number of subjects enrolled | Japan: 150 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 73 |
| Country: Number of subjects enrolled | Poland: 164 |
| Country: Number of subjects enrolled | Russian Federation: 70 |
| Country: Number of subjects enrolled | Taiwan: 11 |
| Country: Number of subjects enrolled | United States: 494 |
| Worldwide total number of subjects | 1740 |
| EEA total number of subjects | 476 |

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) | 868 |
| From 65 to 84 years | 872 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 175 sites in the United States, United Kingdom, Taiwan (TW), South Korea (SK), Russia, Poland, Hungary, Germany, Czech Republic, China, and Japan from April 2015 to August 2017. The entire study period was scheduled to take approximately 30 weeks for each individual subject from the time of screening.

Pre-assignment

Screening details:

Subjects were randomized in a 7:6:6:3 scheme (GFF MDI, FF MDI, GP MDI, and Placebo MDI). Randomization was stratified by reversibility to Ventolin HFA and COPD disease severity (moderate vs severe or very severe) to ensure a similar distribution of treatment arms across stratum.

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 | GFF MDI 14.4/9.6 ug |

Arm description:

Glycopyrronium, Formoterol Fumarate, Metered Dose Inhalation 14.4/9.6 ug

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Glycopyrronium Formoterol Fumarate MDI |
| Investigational medicinal product code | |
| Other name | GFF MDI |
| 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 |
| Pharmaceutical forms | Pressurised inhalation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

Taken as 2 inhalations BID

| | |
|------------------|----------------|
| Arm title | GP MDI 14.4 ug |
|------------------|----------------|

Arm description:

Glycopyrronium 14.4 ug Metered Dose Inhalation

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

| | |
|--|------------------------------------|
| Investigational medicinal product name | Glycopyrronium MDI |
| Investigational medicinal product code | |
| Other name | GP MDI |
| Pharmaceutical forms | Pressurised inhalation, suspension |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Taken as 2 inhalations BID | |
| Arm title | Placebo MDI |

Arm description:

Placebo Metered Dose Inhalation

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo MDI |
| Investigational medicinal product code | |
| Other name | Placebo MDI |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Taken as 2 inhalations BID

| Number of subjects in period 1 | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug |
|---------------------------------------|---------------------|---------------|----------------|
| Started | 551 | 480 | 474 |
| Completed | 491 | 415 | 412 |
| Not completed | 60 | 65 | 62 |
| Physician decision | 1 | 4 | 2 |
| Subject Discretion | 18 | 17 | 23 |
| Adverse event, non-fatal | 15 | 14 | 15 |
| Protocol Specified Criteria | 17 | 12 | 13 |
| Lost to follow-up | 5 | 5 | 3 |
| Lack of efficacy | 3 | 8 | 4 |
| Protocol deviation | 1 | 5 | 2 |

| Number of subjects in period 1 | Placebo MDI |
|---------------------------------------|-------------|
| Started | 235 |
| Completed | 197 |
| Not completed | 38 |
| Physician decision | 2 |
| Subject Discretion | 14 |
| Adverse event, non-fatal | 3 |
| Protocol Specified Criteria | 8 |
| Lost to follow-up | 1 |
| Lack of efficacy | 8 |
| Protocol deviation | 2 |

Baseline characteristics

Reporting groups

| | |
|--|---------------------|
| Reporting group title | GFF MDI 14.4/9.6 ug |
| Reporting group description: Glycopyrronium, Formoterol Fumarate, Metered Dose Inhalation 14.4/9.6 ug | |
| Reporting group title | FF MDI 9.6 ug |
| Reporting group description: Formoterol Fumarate, Metered Dose Inhalation 9.6 ug | |
| Reporting group title | GP MDI 14.4 ug |
| Reporting group description: Glycopyrronium 14.4 ug Metered Dose Inhalation | |
| Reporting group title | Placebo MDI |
| Reporting group description: Placebo Metered Dose Inhalation | |

| Reporting group values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug |
|--|---------------------|---------------|----------------|
| Number of subjects | 551 | 480 | 474 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 261 | 240 | 248 |
| From 65-84 years | 290 | 240 | 226 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 64.7 | 64.1 | 64.0 |
| standard deviation | ± 7.4 | ± 7.6 | ± 8.1 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 143 | 115 | 128 |
| Male | 408 | 365 | 346 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 0 |
| Asian | 223 | 204 | 181 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 12 | 16 | 18 |
| White | 315 | 260 | 275 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |

| Reporting group values | Placebo MDI | Total | |
|---|-------------|-------|--|
| Number of subjects | 235 | 1740 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 119 | 868 | |
| From 65-84 years | 116 | 872 | |
| 85 years and over | 0 | 0 | |
| Age Continuous Units: Years | | | |
| arithmetic mean | 63.9 | | |
| standard deviation | ± 7.5 | - | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 64 | 450 | |
| Male | 171 | 1290 | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | |
| Asian | 92 | 700 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 6 | 52 | |
| White | 137 | 987 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | GFF MDI 14.4/9.6 ug |
| Reporting group description: Glycopyrronium, Formoterol Fumarate, Metered Dose Inhalation 14.4/9.6 ug | |
| Reporting group title | FF MDI 9.6 ug |
| Reporting group description: Formoterol Fumarate, Metered Dose Inhalation 9.6 ug | |
| Reporting group title | GP MDI 14.4 ug |
| Reporting group description: Glycopyrronium 14.4 ug Metered Dose Inhalation | |
| Reporting group title | Placebo MDI |
| Reporting group description: Placebo Metered Dose Inhalation | |

Primary: Change from baseline in morning pre-dose trough FEV1 at week 24 of treatment (US/China approach)

| | |
|--|--|
| End point title | Change from baseline in morning pre-dose trough FEV1 at week 24 of treatment (US/China approach) |
| End point description: For the US/China approach, the primary endpoint was the change from baseline in morning pre-dose trough FEV1 at Week 24 of treatment | |
| End point type | Primary |
| End point timeframe: at week 24 | |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|---------------------|-----------------|-----------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 488 | 413 | 412 | 196 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 120 (102 to 138) | 47 (28 to 67) | 60 (41 to 80) | -45 (-73 to -17) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: Change from baseline in morning pre-dose trough FEV1 (Liters) at Week 24 | |
| Comparison groups | GFF MDI 14.4/9.6 ug v Placebo MDI |

| | |
|---|---------------|
| Number of subjects included in analysis | 684 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.132 |
| upper limit | 0.198 |

| | |
|--|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 (Liters) at Week 24 | |
| Comparison groups | FF MDI 9.6 ug v Placebo MDI |
| Number of subjects included in analysis | 609 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.058 |
| upper limit | 0.126 |

| | |
|--|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 (Liters) at Week 24 | |
| Comparison groups | GP MDI 14.4 ug v Placebo MDI |
| Number of subjects included in analysis | 608 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.071 |
| upper limit | 0.14 |

| | |
|--|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 (Liters) at Week 24 | |
| Comparison groups | GFF MDI 14.4/9.6 ug v FF MDI 9.6 ug |
| Number of subjects included in analysis | 901 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.046 |
| upper limit | 0.099 |

| | |
|--|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 (Liters) at Week 24 | |
| Comparison groups | GFF MDI 14.4/9.6 ug v GP MDI 14.4 ug |
| Number of subjects included in analysis | 900 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.033 |
| upper limit | 0.086 |

| | |
|---|---|
| Primary: Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach | |
| End point title | Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach |
| End point description: | |
| Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach | |
| End point type | Primary |
| End point timeframe: | |
| over weeks 12-24 | |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|---|------------------------|-----------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 517 | 436 | 437 | 205 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 128 (113 to 143) | 54 (38 to 71) | 74 (58 to 91) | -25 (-49 to -1) |

Statistical analyses

| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
|--|---|
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 (Liters) over weeks 12-24, Japan approach | |
| Comparison groups | GFF MDI 14.4/9.6 ug v Placebo MDI |
| Number of subjects included in analysis | 722 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.125 |
| upper limit | 0.181 |

| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
|---|---|
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach | |
| Comparison groups | FF MDI 9.6 ug v Placebo MDI |
| Number of subjects included in analysis | 641 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.05 |
| upper limit | 0.109 |

| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach

| | |
|---|------------------------------|
| Comparison groups | GP MDI 14.4 ug v Placebo MDI |
| Number of subjects included in analysis | 642 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.07 |
| upper limit | 0.128 |

| | |
|---|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach | |
| Comparison groups | GFF MDI 14.4/9.6 ug v FF MDI 9.6 ug |
| Number of subjects included in analysis | 953 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.051 |
| upper limit | 0.096 |

| | |
|---|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | |
| Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach | |
| Comparison groups | GFF MDI 14.4/9.6 ug v GP MDI 14.4 ug |
| Number of subjects included in analysis | 954 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.031 |
| upper limit | 0.076 |

Primary: Change from baseline in morning pre-dose trough FEV1 over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach.

| | |
|-----------------|--|
| End point title | Change from baseline in morning pre-dose trough FEV1 over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach. |
|-----------------|--|

End point description:

Change from baseline in morning pre-dose trough FEV1 over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach.

| | |
|----------------------|---------------|
| End point type | Primary |
| End point timeframe: | over 24 weeks |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|---------------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 541 | 467 | 465 | 225 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 135 (121 to 149) | 63 (48 to 78) | 80 (65 to 94) | -20 (-41 to 2) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | Change from baseline in morning pre-dose trough FEV1 (Liters) over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach. |
| Comparison groups | GFF MDI 14.4/9.6 ug v Placebo MDI |
| Number of subjects included in analysis | 766 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.129 |
| upper limit | 0.18 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: | Change from baseline in morning pre-dose trough FEV1 (Liters) over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach. |

| | |
|---|-----------------------------|
| Comparison groups | FF MDI 9.6 ug v Placebo MDI |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.057 |
| upper limit | 0.109 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
|-----------------------------------|---|

Statistical analysis description:

Change from baseline in morning pre-dose trough FEV1 (Liters) over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach.

| | |
|---|------------------------------|
| Comparison groups | GP MDI 14.4 ug v Placebo MDI |
| Number of subjects included in analysis | 690 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.073 |
| upper limit | 0.125 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
|-----------------------------------|---|

Statistical analysis description:

Change from baseline in morning pre-dose trough FEV1 (Liters) over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach.

| | |
|---|-------------------------------------|
| Comparison groups | GFF MDI 14.4/9.6 ug v FF MDI 9.6 ug |
| Number of subjects included in analysis | 1008 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.052 |
| upper limit | 0.092 |

| | |
|--|---|
| Statistical analysis title | Change from baseline in AM pre-dose trough FEV1 |
| Statistical analysis description: Change from baseline in morning pre-dose trough FEV1 (Liters) over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach. | |
| Comparison groups | GFF MDI 14.4/9.6 ug v GP MDI 14.4 ug |
| Number of subjects included in analysis | 1006 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Confidence interval | |
| level | Other: 0.95 % |
| sides | 2-sided |
| lower limit | 0.035 |
| upper limit | 0.076 |

Secondary: TDI focal score over 24 weeks, US/China and EU/SK/TW Approach

| | |
|---|---|
| End point title | TDI focal score over 24 weeks, US/China and EU/SK/TW Approach |
| End point description: TDI Focal Score over 24 weeks, US/China and EU/SK/TW Approach | |
| End point type | Secondary |
| End point timeframe: over 24 Weeks | |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|------------------------|------------------|-------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 532 | 458 | 457 | 217 |
| Units: Score | | | | |
| least squares mean (confidence interval 95%) | 1.6 (1.4 to 1.8) | 1.5 (1.3 to 1.7) | 1.3 (1.1 to 1.5) | 0.8 (0.5 to 1.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: TDI focal score over Weeks 12-24 Japan approach

| | |
|-----------------|---|
| End point title | TDI focal score over Weeks 12-24 Japan approach |
|-----------------|---|

| | |
|---|-----------|
| End point description: TDI Focal Score over Weeks 12-24 Japan approach | |
| End point type | Secondary |
| End point timeframe: over Weeks 12-24 | |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|------------------------|------------------|-------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 515 | 434 | 436 | 205 |
| Units: Scores | | | | |
| least squares mean (confidence interval 95%) | 1.7 (1.5 to 1.9) | 1.5 (1.3 to 1.7) | 1.4 (1.2 to 1.6) | 0.8 (0.5 to 1.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: TDI focal score over 24 weeks - US/China and EU/SK/TW approaches - Symptomatic Population

| | |
|---|--|
| End point title | TDI focal score over 24 weeks - US/China and EU/SK/TW approaches -Symptomatic Population |
| End point description: TDI Focal Score – Secondary Endpoints, US/China and EU/SK/TW approaches | |
| End point type | Secondary |
| End point timeframe: over 24 Weeks | |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|------------------------|------------------|-------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 244 | 217 | 228 | 108 |
| Units: Scores | | | | |
| least squares mean (confidence interval 95%) | 1.5 (1.2 to 1.7) | 1.3 (1.0 to 1.6) | 1.1 (0.8 to 1.3) | 0.7 (0.3 to 1.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: TDI focal score over weeks 12-24 - Japan approach - Symptomatic Population

| | |
|-----------------|---|
| End point title | TDI focal score over weeks 12-24 - Japan approach - |
|-----------------|---|

End point description:

TDI Focal Score – Secondary Endpoint, Japan approach

End point type Secondary

End point timeframe:

over weeks 12-24

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|---|------------------------|------------------|-------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 237 | 200 | 218 | 97 |
| Units: Scores | | | | |
| least squares mean (confidence interval 95%) | 1.5 (1.2 to 1.8) | 1.4 (1.0 to 1.7) | 1.1 (0.8 to 1.4) | 0.7 (0.2 to 1.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Peak change from baseline in FEV1 within 2 hours post-dosing at Week 24 US/China approach

End point title Peak change from baseline in FEV1 within 2 hours post-dosing at Week 24 US/China approach

End point description:

Peak change from baseline in FEV1 within 2 hours post-dosing at Week 24 US/China approach

End point type Secondary

End point timeframe:

at week 24

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|---|------------------------|---------------------|---------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 490 | 413 | 412 | 196 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 358 (338 to 378) | 247 (226 to 269) | 214 (192 to 235) | 55 (24 to 87) |

Statistical analyses

No statistical analyses for this end point

Secondary: Peak change from baseline in FEV1 within 2 hours post-dosing over weeks 12-24 Japan approach

| | |
|------------------------|--|
| End point title | Peak change from baseline in FEV1 within 2 hours post-dosing over weeks 12-24 Japan approach |
| End point description: | Peak change from baseline in FEV1 within 2 hours post-dosing over weeks 12-24 Japan approach |
| End point type | Secondary |
| End point timeframe: | over weeks 12-24 |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|------------------------|------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 516 | 436 | 436 | 205 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 368 (350 to 386) | 255 (236 to 274) | 228 (209 to 248) | 70 (42 to 98) |

Statistical analyses

No statistical analyses for this end point

Secondary: Peak change from baseline in FEV1 within 2 hours post-dosing over 24 weeks EU/SK/TW approach

| | |
|------------------------|--|
| End point title | Peak change from baseline in FEV1 within 2 hours post-dosing over 24 weeks EU/SK/TW approach |
| End point description: | Peak change from baseline in FEV1 within 2 hours post-dosing over 24 weeks EU/SK/TW approach |
| End point type | Secondary |
| End point timeframe: | over 24 weeks |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|------------------------|------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 550 | 480 | 474 | 235 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 375 (360 to 389) | 277 (261 to 293) | 234 (218 to 250) | 82 (58 to 105) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SGRQ Total Score at week 24, US/China

approach

| | |
|-----------------|--|
| End point title | Change from Baseline in SGRQ Total Score at week 24, US/China approach |
|-----------------|--|

End point description:

Change from Baseline in SGRQ Total Score at week 24, US/China approach

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

End point timeframe:

at week 24

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|---------------------|---------------------|---------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 489 | 415 | 412 | 196 |
| Units: Units | | | | |
| least squares mean (confidence interval 95%) | -5.3 (-6.4 to -4.2) | -5.6 (-6.8 to -4.4) | -3.7 (-4.8 to -2.5) | -0.9 (-2.6 to 0.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SGRQ Total Score over weeks 12-24 , Japan & EU/SK/TW approach

| | |
|-----------------|---|
| End point title | Change from Baseline in SGRQ Total Score over weeks 12-24 , Japan & EU/SK/TW approach |
|-----------------|---|

End point description:

Change from Baseline in SGRQ Total Score over weeks 12-24 , Japan & EU/SK/TW approach

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

End point timeframe:

over weeks 12-24

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 516 | 436 | 436 | 205 |
| Units: Units | | | | |
| least squares mean (confidence interval 95%) | -5.2 (-6.1 to -4.3) | -5.0 (-5.9 to -4.0) | -3.6 (-4.6 to -2.6) | -1.7 (-3.1 to -0.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SGRQ Total Score at week 24 in Symptomatic Population, US/China approach

| | |
|--|--|
| End point title | Change from Baseline in SGRQ Total Score at week 24 in Symptomatic Population, US/China approach |
| End point description: Change from Baseline in SGRQ Total Score at week 24 in Symptomatic Population, US/China approach | |
| End point type | Secondary |
| End point timeframe: at week 24 | |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|------------------------|---------------------|---------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 220 | 189 | 202 | 92 |
| Units: Units | | | | |
| least squares mean (confidence interval 95%) | -6.9 (-8.6 to -5.2) | -7.8 (-9.7 to -5.9) | -3.8 (-5.6 to -2.0) | -1.6 (-4.3 to 1.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SGRQ Total Score over weeks 12-24, in Symptomatic Population, Japan & EU/SK/TW approach

| | |
|---|---|
| End point title | Change from Baseline in SGRQ Total Score over weeks 12-24, in Symptomatic Population, Japan & EU/SK/TW approach |
| End point description: Change from Baseline in SGRQ Total Score over weeks 12-24, in Symptomatic Population, Japan & EU/SK/TW approach | |
| End point type | Secondary |
| End point timeframe: over weeks 12-24 | |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|--|------------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 237 | 200 | 218 | 97 |
| Units: Units | | | | |
| least squares mean (confidence interval 95%) | -6.9 (-8.4 to -5.4) | -7.3 (-8.9 to -5.6) | -3.9 (-5.5 to -2.4) | -3.1 (-5.4 to -0.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in average daily rescue Ventolin use over 24 weeks in RVU population, all approaches

| | |
|-----------------|---|
| End point title | Change from baseline in average daily rescue Ventolin use over 24 weeks in RVU population, all approaches |
|-----------------|---|

End point description:

Change from baseline in average daily rescue Ventolin use over 24 weeks in RVU population, all approaches

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

End point timeframe:

over 24 weeks

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|---|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 256 | 232 | 225 | 109 |
| Units: Puffs/day | | | | |
| least squares mean (confidence interval 95%) | -1.4 (-1.7 to - 1.1) | -1.0 (-1.3 to - 0.7) | -0.6 (-0.9 to - 0.3) | -0.4 (-0.8 to - 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of action on Day 1 - 5 Minutes Post-Dose, all approaches

| | |
|-----------------|--|
| End point title | Time to onset of action on Day 1 - 5 Minutes Post-Dose, all approaches |
|-----------------|--|

End point description:

Time to onset of action on Day 1 - 5 Minutes Post-Dose, all approaches

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

End point timeframe:

Day 1

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|---|------------------------|---------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 464 | 406 | 403 | 197 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 202 (191 to 212) | 186 (175 to 197) | 59 (48 to 70) | 22 (6 to 38) |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of action on Day 1 - 15 Minutes Post-Dose, all approaches

| | |
|------------------------|---|
| End point title | Time to onset of action on Day 1 - 15 Minutes Post-Dose, all approaches |
| End point description: | Time to onset of action on Day 1 - 15 Minutes Post-Dose, all approaches |
| End point type | Secondary |
| End point timeframe: | Day 1 |

| End point values | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug | Placebo MDI |
|---|------------------------|---------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 530 | 458 | 453 | 229 |
| Units: mL | | | | |
| least squares mean (confidence interval 95%) | 241 (230 to 252) | 220 (208 to 231) | 105 (93 to 117) | 33 (16 to 50) |

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 consent throughout the four treatment periods of 24 weeks and up to 10 days following the last dose of study drug.

Adverse event reporting additional description:

The Safety Population was defined as all subjects who were randomized to treatment regardless and received at least one dose of study treatment. Serious adverse events collected from the time the subject signed consent up to 14 days following the last dose of study drug.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | GFF MDI 14.4/9.6 ug |
|-----------------------|---------------------|

Reporting group description:

Glycopyrronium, Formoterol Fumarate, Metered Dose Inhalation 14.4/9.6 ug

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

Reporting group description:

Formoterol Fumarate, Metered Dose Inhalation 9.6 ug

| | |
|-----------------------|----------------|
| Reporting group title | GP MDI 14.4 ug |
|-----------------------|----------------|

Reporting group description:

Glycopyrronium 14.4 ug Metered Dose Inhalation

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

Reporting group description:

Placebo Metered Dose Inhalation

| Serious adverse events | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug |
|---|---------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 53 / 551 (9.62%) | 40 / 480 (8.33%) | 34 / 474 (7.17%) |
| number of deaths (all causes) | 1 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Breast neoplasm | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cardiac myxoma | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Haemangiopericytoma | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Laryngeal cancer | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to liver | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Papillary thyroid cancer | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| 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 disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 551 (0.36%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Allergy to arthropod sting | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |

| | | | |
|---|------------------|------------------|------------------|
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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, thoracic and mediastinal disorders | | | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 16 / 551 (2.90%) | 13 / 480 (2.71%) | 12 / 474 (2.53%) |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 13 | 0 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma-chronic obstructive pulmonary disease overlap syndrome | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Cough | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Dyspnoea Exertional | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somatic symptom disorder | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Injury, poisoning and procedural complications | | | |
| Humeral fracture | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Head injury | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural hypotension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 2 / 474 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 2 / 480 (0.42%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 chronic | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Nervous system disorders | | | |
| Carotid artery disease | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| 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 | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hypoglycemic coma | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudoradicular syndrome | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 | | | |
| Angel closure glaucoma | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 2 / 474 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Colitis ischemic | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Dysphagia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Glomerulonephritis | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 | | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondyloarthropathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 551 (1.27%) | 2 / 480 (0.42%) | 3 / 474 (0.63%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 551 (0.54%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung Infection | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 2 / 480 (0.42%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (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 |
| Borrelia Infection | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 1 / 480 (0.21%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes Zoster | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes melitus | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 1 / 474 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 551 (0.18%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obesity | | | |
| subjects affected / exposed | 0 / 551 (0.00%) | 0 / 480 (0.00%) | 0 / 474 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------|-------------|--|--|
| Serious adverse events | Placebo MDI | | |
|-------------------------------|-------------|--|--|

| | | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 235 (8.09%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Breast neoplasm | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac myxoma | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon adenoma | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemangiopericytoma | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngeal cancer | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to liver | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|--|--|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Allergy to arthropod sting | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 7 / 235 (2.98%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma-chronic obstructive pulmonary disease overlap syndrome | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea Exertional | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somatic symptom disorder | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Humerous fracture | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Procedural hypotension | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Carotid artery disease | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycemic coma | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudoradicular syndrome | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Gastrointestinal haemorrhage subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ischemic subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Food poisoning subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer haemorrhage subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoids thrombosed subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glomerulonephritis | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue | | | |

| | | | | |
|---|-----------------|--|--|--|
| disorders | | | | |
| Intervertebral disc degeneration | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pathological fracture | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal osteoarthritis | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spondyloarthropathy | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 3 / 235 (1.28%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung Infection | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchiolitis | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|-----------------|--|--|--|
| Borrelia Infection | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal Infection | | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatitis C | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes Zoster | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post procedural infection | | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |

| | | | |
|---|-----------------|--|--|
| Diabetes melitus | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obesity | | | |
| subjects affected / exposed | 1 / 235 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | GFF MDI 14.4/9.6 ug | FF MDI 9.6 ug | GP MDI 14.4 ug |
|---|---------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 166 / 551 (30.13%) | 123 / 480 (25.63%) | 128 / 474 (27.00%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 16 / 551 (2.90%) | 13 / 480 (2.71%) | 12 / 474 (2.53%) |
| occurrences (all) | 16 | 13 | 12 |
| Cough | | | |
| subjects affected / exposed | 13 / 551 (2.36%) | 8 / 480 (1.67%) | 10 / 474 (2.11%) |
| occurrences (all) | 14 | 8 | 11 |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 551 (2.00%) | 7 / 480 (1.46%) | 6 / 474 (1.27%) |
| occurrences (all) | 11 | 7 | 8 |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain | | | |
| subjects affected / exposed | 15 / 551 (2.72%) | 5 / 480 (1.04%) | 7 / 474 (1.48%) |
| occurrences (all) | 16 | 5 | 7 |
| Infections and infestations | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 50 / 551 (9.07%) 56 | 46 / 480 (9.58%) 52 | 44 / 474 (9.28%) 55 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 37 / 551 (6.72%) 44 | 29 / 480 (6.04%) 34 | 33 / 474 (6.96%) 40 |
| Pneumonia subjects affected / exposed occurrences (all) | 9 / 551 (1.63%) 9 | 5 / 480 (1.04%) 5 | 5 / 474 (1.05%) 5 |
| Bronchitis subjects affected / exposed occurrences (all) | 4 / 551 (0.73%) 5 | 6 / 480 (1.25%) 7 | 8 / 474 (1.69%) 8 |
| Pharyngitis subjects affected / exposed occurrences (all) | 11 / 551 (2.00%) 11 | 4 / 480 (0.83%) 4 | 3 / 474 (0.63%) 3 |

| | | | |
|---|----------------------|--|--|
| Non-serious adverse events | Placebo MDI | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 61 / 235 (25.96%) | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 7 / 235 (2.98%) 7 | | |
| Cough subjects affected / exposed occurrences (all) | 2 / 235 (0.85%) 3 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 7 / 235 (2.98%) 7 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain subjects affected / exposed occurrences (all) | 1 / 235 (0.43%) 1 | | |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |

| | | | |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed | 16 / 235 (6.81%) | | |
| occurrences (all) | 17 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 20 / 235 (8.51%) | | |
| occurrences (all) | 24 | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 235 (2.55%) | | |
| occurrences (all) | 6 | | |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 235 (2.13%) | | |
| occurrences (all) | 5 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 235 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 18 December 2014 | Updated registration approaches to Include Japan. Updated inclusion/exclusion criteria. Clarification of COP exacerbation. |
| 08 April 2015 | Updated inclusion criteria. |
| 20 April 2015 | Updated number of estimated number of sites. Clarification of approaches. Clarify and standardize reporting of COPD language. Update of statistical methods in synopsis. |
| 01 May 2015 | Updated inclusion criteria, specifications for EU specific text. |
| 20 January 2017 | Revised sponsor contact name. Clarified use of ITT population vs symptomatic and rescue ventolin user populations. Clarified TDI language. Updated endpoints. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported