

**Clinical trial results:****A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 Compared to PT005, PT008, and Open-label Symbicort® Turbuhaler®, as an Active Control, on Lung Function over a 24-Week Treatment Period in Subjects With Moderate to Very Severe COPD****Summary**

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-000154-34   |
| Trial protocol           | CZ HU DE PL      |
| Global end of trial date | 30 November 2017 |

**Results information**

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

**Trial information****Trial identification**

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | PT009002 |
|-----------------------|----------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02766608 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Pearl Therapeutics, a Member of the AstraZeneca Group   |
| Sponsor organisation address | 200 Cardinal Way, Redwood City, United States, 94063  |
| Public contact               | Paul M. Dorinsky, MD, Pearl Therapeutics, a Member of the AstraZeneca Group, 1 6503052600, paul.dorinsky1@astrazeneca.com |
| Scientific contact           | Paul M. Dorinsky, MD, Pearl Therapeutics, a Member of the AstraZeneca Group, 1 6503052600, paul.dorinsky1@astrazeneca.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 30 November 2017 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 30 November 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 November 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 assess the effects of BFF MDI relative to FF MDI and BD MDI on lung function

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                          | 31 May 2016 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Canada: 107             |
| Country: Number of subjects enrolled | Czech Republic: 208     |
| Country: Number of subjects enrolled | Germany: 135            |
| Country: Number of subjects enrolled | Hungary: 201            |
| Country: Number of subjects enrolled | Poland: 310             |
| Country: Number of subjects enrolled | Russian Federation: 384 |
| Country: Number of subjects enrolled | United States: 1016     |
| Worldwide total number of subjects   | 2361                    |
| EEA total number of subjects         | 854                     |

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)      | 1132 |
| From 65 to 84 years       | 1229 |
| 85 years and over         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

This study randomized subjects at 244 study centers in 7 countries, from June 2016 and November 2017. The study period was scheduled to take up to approximately 30 weeks for each individual subject from the time of screening through the follow-up period.

### Pre-assignment

Screening details:

Subjects were randomized in a 3:3:3:1:1 ratio to BFF 320/9.6, BFF 160/9.6, FF 9.6, BD 320, and Symbicort.

### 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 |

Blinding implementation details:

Subjects assigned to blinded study drug will be instructed to dose while at home from the site-primed MDI only, unless all of the following replacement conditions are met: o Dose indicator is in the red zone (Refer to Appendix 1 for dose indicator reading instructions) o The dose indicator registers  $\leq 10$  puffs remaining, and o Their next scheduled study clinic visit is not the following day

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | BFF MDI 320/9.6 $\mu\text{g}$ |

Arm description:

Budesonide Formoterol Fumarate Metered Dose Inhalation 320/9.6  $\mu\text{g}$

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

Dosage and administration details:

Taken as 2 inhalations BID

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | BFF MDI 160/9.6 $\mu\text{g}$ |
|------------------|-------------------------------|

Arm description:

Budesonide Formoterol Fumarate Metered Dose Inhalation 160/9.6  $\mu\text{g}$

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

Dosage and administration details:

Taken as 2 inhalations BID

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | FF MDI 9.6 $\mu\text{g}$ |
|------------------|--------------------------|

Arm description:

Formoterol Fumarate Metered Dose Inhalation 9.6  $\mu\text{g}$

|          |              |
|----------|--------------|
| 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:<br>Taken as 2 inhalations BID |                                    |
| <b>Arm title</b>   | BD MDI 320 µg                      |

Arm description:

Budesonide Metered Dose Inhalation 320 µg

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | Budesonide MDI                     |
| Investigational medicinal product code |                                    |
| Other name                             | BD MDI                             |
| Pharmaceutical forms                   | Pressurised inhalation, suspension |
| Routes of administration               | Inhalation use                     |

Dosage and administration details:

Taken as 2 inhalations

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Symbicort TBH 400/12 µg |
|------------------|-------------------------|

Arm description:

Symbicort Turbuhaler 400/12 µg

|  |                                    |
|--|------------------------------------|
| Arm type                               | Active control                     |
| Investigational medicinal product name | Symbicort Turbuhaler               |
| Investigational medicinal product code |                                    |
| Other name                             | Symbicort                          |
| Pharmaceutical forms                   | Pressurised inhalation, suspension |
| Routes of administration               | Inhalation use                     |

Dosage and administration details:

Taken as 2 inhalations BID

| <b>Number of subjects in period 1</b> | BFF MDI 320/9.6 µg | BFF MDI 160/9.6 µg | FF MDI 9.6 µg |
|---------------------------------------|--------------------|--------------------|---------------|
| Started                               | 655                | 637                | 644           |
| Completed                             | 576                | 567                | 554           |
| Not completed                         | 79                 | 70                 | 90            |
| Administrative Reasons                | 3                  | 1                  | 1             |
| Consent withdrawn by subject          | 21                 | 20                 | 24            |
| Physician decision                    | 3                  | 2                  | 3             |
| Adverse event, non-fatal              | 27                 | 22                 | 17            |
| Protocol disc criteria                | 3                  | 3                  | 4             |
| Lost to follow-up                     | 6                  | 3                  | 5             |
| Lack of efficacy                      | 16                 | 15                 | 32            |
| Protocol deviation                    | -                  | 4                  | 4             |

|                                       |               |                         |
|---------------------------------------|---------------|-------------------------|
| <b>Number of subjects in period 1</b> | BD MDI 320 µg | Symbicort TBH 400/12 µg |
|---------------------------------------|---------------|-------------------------|

|                              |     |     |
|------------------------------|-----|-----|
| Started                      | 206 | 219 |
| Completed                    | 169 | 190 |
| Not completed                | 37  | 29  |
| Administrative Reasons       | -   | -   |
| Consent withdrawn by subject | 13  | 10  |
| Physician decision           | 1   | 2   |
| Adverse event, non-fatal     | 13  | 12  |
| Protocol disc criteria       | -   | -   |
| Lost to follow-up            | 2   | 2   |
| Lack of efficacy             | 8   | 2   |
| Protocol deviation           | -   | 1   |

## Baseline characteristics

### Reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | BFF MDI 320/9.6 µg      |
| Reporting group description:<br>Budesonide Formoterol Fumarate Metered Dose Inhalation 320/9.6 µg |                         |
| Reporting group title   | BFF MDI 160/9.6 µg      |
| Reporting group description:<br>Budesonide Formoterol Fumarate Metered Dose Inhalation 160/9.6 µg |                         |
| Reporting group title   | FF MDI 9.6 µg           |
| Reporting group description:<br>Formoterol Fumarate Metered Dose Inhalation 9.6 µg                |                         |
| Reporting group title   | BD MDI 320 µg           |
| Reporting group description:<br>Budesonide Metered Dose Inhalation 320 µg                         |                         |
| Reporting group title   | Symbicort TBH 400/12 µg |
| Reporting group description:<br>Symbicort Turbuhaler 400/12 µg                                    |                         |

| Reporting group values                    | BFF MDI 320/9.6 µg | BFF MDI 160/9.6 µg | FF MDI 9.6 µg |
|---|--------------------|--------------------|---------------|
| Number of subjects                        | 655                | 637                | 644           |
| Age categorical                           |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| Adults (18-64 years)                      | 322                | 298                | 313           |
| From 65-84 years                          | 333                | 339                | 331           |
| Age Continuous                            |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: years                              |                    |                    |               |
| least squares mean                        | 64.2               | 64.3               | 64.1          |
| standard deviation                        | ± 7.7              | ± 7.6              | ± 8.0         |
| Sex: Female, Male                         |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| Female                                    | 253                | 260                | 261           |
| Male                                      | 402                | 377                | 383           |
| Ethnicity (NIH/OMB)                       |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| Hispanic or Latino                        | 16                 | 18                 | 21            |
| Not Hispanic or Latino                    | 637                | 616                | 623           |
| Unknown or Not Reported                   | 2                  | 3                  | 0             |
| Race (NIH/OMB)                            |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| American Indian or Alaska Native          | 2                  | 2                  | 2             |
| Asian                                     | 1                  | 1                  | 0             |
| Native Hawaiian or Other Pacific Islander | 0                  | 0                  | 0             |
| Black or African American                 | 19                 | 15                 | 20            |

|                         |     |     |     |
|-------------------------|-----|-----|-----|
| White                   | 633 | 619 | 622 |
| More than one race      | 0   | 0   | 0   |
| Unknown or Not Reported | 0   | 0   | 0   |

| <b>Reporting group values</b>             | BD MDI 320 µg | Symbicort TBH 400/12 µg | Total |
|---|---------------|-------------------------|-------|
| Number of subjects                        | 206           | 219                     | 2361  |
| Age categorical                           |               |                         |       |
| mITT Population                           |               |                         |       |
| Units: Subjects                           |               |                         |       |
| Adults (18-64 years)                      | 101           | 98                      | 1132  |
| From 65-84 years                          | 105           | 121                     | 1229  |
| Age Continuous                            |               |                         |       |
| mITT Population                           |               |                         |       |
| Units: years                              |               |                         |       |
| least squares mean                        | 64.2          | 65.3                    |       |
| standard deviation                        | ± 7.4         | ± 7.0                   | -     |
| Sex: Female, Male                         |               |                         |       |
| mITT Population                           |               |                         |       |
| Units: Subjects                           |               |                         |       |
| Female                                    | 81            | 78                      | 933   |
| Male                                      | 125           | 141                     | 1428  |
| Ethnicity (NIH/OMB)                       |               |                         |       |
| mITT Population                           |               |                         |       |
| Units: Subjects                           |               |                         |       |
| Hispanic or Latino                        | 8             | 6                       | 69    |
| Not Hispanic or Latino                    | 198           | 212                     | 2286  |
| Unknown or Not Reported                   | 0             | 1                       | 6     |
| Race (NIH/OMB)                            |               |                         |       |
| Units: Subjects                           |               |                         |       |
| American Indian or Alaska Native          | 0             | 0                       | 6     |
| Asian                                     | 0             | 1                       | 3     |
| Native Hawaiian or Other Pacific Islander | 0             | 0                       | 0     |
| Black or African American                 | 9             | 8                       | 71    |
| White                                     | 197           | 210                     | 2281  |
| More than one race                        | 0             | 0                       | 0     |
| Unknown or Not Reported                   | 0             | 0                       | 0     |

### Subject analysis sets

|   |                             |
|---|-----------------------------|
| Subject analysis set title  | BFF MDI 320/9.6 µg          |
| Subject analysis set type   | Modified intention-to-treat |
| Subject analysis set description:                                 |                             |
| Budesonide Formoterol Fumarate Metered Dose Inhalation 320/9.6 µg |                             |
| Subject analysis set title  | BFF MDI 160/9.6 µg          |
| Subject analysis set type   | Modified intention-to-treat |
| Subject analysis set description:                                 |                             |
| Budesonide Formoterol Fumarate Metered Dose Inhalation 160/9.6 µg |                             |
| Subject analysis set title  | FF MDI 9.6 µg               |
| Subject analysis set type   | Modified intention-to-treat |

Subject analysis set description:

Formoterol Fumarate Metered Dose Inhalation 9.6 µg

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | BD MDI 320 µg               |
| Subject analysis set type  | Modified intention-to-treat |

Subject analysis set description:

Budesonide Metered Dose Inhalation 320 µg

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Symbicort TBH 400/12 ug     |
| Subject analysis set type  | Modified intention-to-treat |

Subject analysis set description:

Symbicort Turbuhaler 400/12 ug

| Reporting group values                    | BFF MDI 320/9.6 µg | BFF MDI 160/9.6 µg | FF MDI 9.6 µg |
|---|--------------------|--------------------|---------------|
| Number of subjects                        | 664                | 649                | 648           |
| Age categorical                           |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| Adults (18-64 years)                      | 322                | 298                | 313           |
| From 65-84 years                          | 333                | 339                | 331           |
| Age Continuous                            |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: years                              |                    |                    |               |
| least squares mean                        | 64.2               | 64.3               | 64.1          |
| standard deviation                        | ± 7.7              | ± 7.6              | ± 8.0         |
| Sex: Female, Male                         |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| Female                                    | 253                | 260                | 261           |
| Male                                      | 402                | 377                | 383           |
| Ethnicity (NIH/OMB)                       |                    |                    |               |
| mITT Population                           |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| Hispanic or Latino                        | 16                 | 18                 | 21            |
| Not Hispanic or Latino                    | 637                | 616                | 623           |
| Unknown or Not Reported                   | 2                  | 3                  | 0             |
| Race (NIH/OMB)                            |                    |                    |               |
| Units: Subjects                           |                    |                    |               |
| American Indian or Alaska Native          | 2                  | 2                  | 2             |
| Asian                                     | 1                  | 1                  | 0             |
| Native Hawaiian or Other Pacific Islander | 0                  | 0                  | 0             |
| Black or African American                 | 19                 | 15                 | 20            |
| White                                     | 633                | 619                | 622           |
| More than one race                        | 0                  | 0                  | 0             |
| Unknown or Not Reported                   | 0                  | 0                  | 0             |

| Reporting group values | BD MDI 320 µg | Symbicort TBH 400/12 ug |  |
|------------------------|---------------|-------------------------|--|
| Number of subjects     | 209           | 219                     |  |
| Age categorical        |               |                         |  |
| mITT Population        |               |                         |  |
| Units: Subjects        |               |                         |  |
| Adults (18-64 years)   | 101           | 98                      |  |

|                  |     |     |  |
|------------------|-----|-----|--|
| From 65-84 years | 105 | 121 |  |
|------------------|-----|-----|--|

|   |       |       |  |
|---|-------|-------|--|
| Age Continuous                            |       |       |  |
| mITT Population                           |       |       |  |
| Units: years                              |       |       |  |
| least squares mean                        | 64.2  | 65.3  |  |
| standard deviation                        | ± 7.4 | ± 7.0 |  |
| Sex: Female, Male                         |       |       |  |
| mITT Population                           |       |       |  |
| Units: Subjects                           |       |       |  |
| Female                                    | 81    | 78    |  |
| Male                                      | 125   | 141   |  |
| Ethnicity (NIH/OMB)                       |       |       |  |
| mITT Population                           |       |       |  |
| Units: Subjects                           |       |       |  |
| Hispanic or Latino                        | 8     | 6     |  |
| Not Hispanic or Latino                    | 198   | 212   |  |
| Unknown or Not Reported                   | 0     | 1     |  |
| Race (NIH/OMB)                            |       |       |  |
| Units: Subjects                           |       |       |  |
| American Indian or Alaska Native          | 0     | 0     |  |
| Asian                                     | 0     | 1     |  |
| Native Hawaiian or Other Pacific Islander | 0     | 0     |  |
| Black or African American                 | 9     | 8     |  |
| White                                     | 197   | 210   |  |
| More than one race                        | 0     | 0     |  |
| Unknown or Not Reported                   | 0     | 0     |  |

## End points

### End points reporting groups

|                                   |   |
|-----------------------------------|---|
| Reporting group title             | BFF MDI 320/9.6 µg  |
| Reporting group description:      | Budesonide Formoterol Fumarate Metered Dose Inhalation 320/9.6 µg |
| Reporting group title             | BFF MDI 160/9.6 µg  |
| Reporting group description:      | Budesonide Formoterol Fumarate Metered Dose Inhalation 160/9.6 µg |
| Reporting group title             | FF MDI 9.6 µg   |
| Reporting group description:      | Formoterol Fumarate Metered Dose Inhalation 9.6 µg                |
| Reporting group title             | BD MDI 320 µg   |
| Reporting group description:      | Budesonide Metered Dose Inhalation 320 µg                         |
| Reporting group title             | Symbicort TBH 400/12 µg   |
| Reporting group description:      | Symbicort Turbuhaler 400/12 µg                                    |
| Subject analysis set title        | BFF MDI 320/9.6 µg  |
| Subject analysis set type         | Modified intention-to-treat                                       |
| Subject analysis set description: | Budesonide Formoterol Fumarate Metered Dose Inhalation 320/9.6 µg |
| Subject analysis set title        | BFF MDI 160/9.6 µg  |
| Subject analysis set type         | Modified intention-to-treat                                       |
| Subject analysis set description: | Budesonide Formoterol Fumarate Metered Dose Inhalation 160/9.6 µg |
| Subject analysis set title        | FF MDI 9.6 µg   |
| Subject analysis set type         | Modified intention-to-treat                                       |
| Subject analysis set description: | Formoterol Fumarate Metered Dose Inhalation 9.6 µg                |
| Subject analysis set title        | BD MDI 320 µg   |
| Subject analysis set type         | Modified intention-to-treat                                       |
| Subject analysis set description: | Budesonide Metered Dose Inhalation 320 µg                         |
| Subject analysis set title        | Symbicort TBH 400/12 ug   |
| Subject analysis set type         | Modified intention-to-treat                                       |
| Subject analysis set description: | Symbicort Turbuhaler 400/12 ug                                    |

### Primary: Change from baseline in morning pre-dose trough FEV1 over 24 weeks (BFF MDI versus FF MDI)

|                        |   |
|------------------------|---|
| End point title        | Change from baseline in morning pre-dose trough FEV1 over 24 weeks (BFF MDI versus FF MDI)  |
| End point description: | Change from baseline in morning pre-dose trough FEV1 (Forced expiratory volume in 1 second) over 24 weeks (BFF MDI versus FF MDI) |
| End point type         | Primary   |
| End point timeframe:   | over 24 weeks   |

|  |                        |                        |                        |                           |
|--|------------------------|------------------------|------------------------|---------------------------|
| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg             |
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group           |
| Number of subjects analysed                  | 627                    | 615                    | 613                    | 190                       |
| Units: Liter                                 |                        |                        |                        |                           |
| least squares mean (confidence interval 95%) | 0.058 (0.045 to 0.071) | 0.033 (0.020 to 0.047) | 0.027 (0.014 to 0.041) | -0.029 (-0.053 to -0.004) |

|  |                            |  |  |  |
|--|----------------------------|--|--|--|
| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 211                        |  |  |  |
| Units: Liter                                 |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.067 (0.044 to 0.090)     |  |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>                 | Baseline morning pre-dose FEV1 over 24 wks                              |
| Statistical analysis description:                 |   |
| Primary endpoint analysis - BFF MDI versus FF MDI |   |
| Comparison groups                                 | BFF MDI 320/9.6 µg v BFF MDI 160/9.6 µg v FF MDI 9.6 µg v BD MDI 320 µg |
| Number of subjects included in analysis           | 2045  |
| Analysis specification                            | Pre-specified   |
| Analysis type                                     | superiority   |
| P-value   | < 0.05  |
| Method  | repeated measures linear mixed model                                    |

|   |  |
|---|--|
| <b>Statistical analysis title</b>                       | Baseline morning pre-dose FEV1 over 24wks    |
| Statistical analysis description:                       |  |
| Primary endpoint BFF 320/9.6 vs Symbicort TBH 400/12 ug |  |
| Comparison groups                                       | BFF MDI 320/9.6 µg v Symbicort TBH 400/12 µg |
| Number of subjects included in analysis                 | 838  |
| Analysis specification                                  | Pre-specified                                |
| Analysis type   | non-inferiority                              |
| Method  | repeated measures linear mixed model         |
| Parameter estimate                                      | LS Mean Difference                           |
| Point estimate  | -0.009                                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.036  |
| upper limit         | 0.018   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Baseline morning pre-dose FEV1 over 24wks |
|-----------------------------------|---|

Statistical analysis description:

Primary endpoint BFF 160/9.6 vs Symbicort 400/12 ug

|   |  |
|---|--|
| Comparison groups                       | BFF MDI 160/9.6 µg v Symbicort TBH 400/12 µg |
| Number of subjects included in analysis | 826  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | non-inferiority                              |
| Method                                  | repeated measures linear mixed model         |
| Parameter estimate                      | LS Mean Difference                           |
| Point estimate                          | -0.034                                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.061  |
| upper limit         | -0.007  |

**Primary: Change from baseline in FEV1 AUC0-4 (BFF MDI vs BD MDI)**

|                 |   |
|-----------------|---|
| End point title | Change from baseline in FEV1 AUC0-4 (BFF MDI vs BD MDI) |
|-----------------|---|

End point description:

Change from baseline in FEV1 (Forced Expiratory Volume) AUC0-4 (Area under the curve from 0 to 4 hours) (BFF MDI vs BD MDI)

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

over 24 weeks

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 654                    | 636                    | 643                    | 206                    |
| Units: Liter                                 |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.211 (0.198 to 0.223) | 0.195 (0.183 to 0.208) | 0.188 (0.176 to 0.201) | 0.030 (0.008 to 0.052) |

|                         |                            |  |  |  |
|-------------------------|----------------------------|--|--|--|
| <b>End point values</b> | Symbicort TBH<br>400/12 µg |  |  |  |
|-------------------------|----------------------------|--|--|--|

|  |                        |  |  |  |
|--|------------------------|--|--|--|
| Subject group type                           | Reporting group        |  |  |  |
| Number of subjects analysed                  | 218                    |  |  |  |
| Units: Liter                                 |                        |  |  |  |
| least squares mean (confidence interval 95%) | 0.202 (0.181 to 0.224) |  |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | FEV1 AUC0-4   |
| Statistical analysis description:  |   |
| Primary endpoint analysis Change from baseline in FEV1 AUC0-4: BFF vs BD |   |
| Comparison groups  | BFF MDI 320/9.6 µg v BFF MDI 160/9.6 µg v FF MDI 9.6 µg v BD MDI 320 µg |
| Number of subjects included in analysis                                  | 2139  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | < 0.05  |
| Method   | repeated measures linear mixed model                                    |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | FEV1 AUC0-4                                  |
| Statistical analysis description:   |  |
| Primary endpoint analysis -Change from baseline in FEV1 AUC0-4: BFF 320/9.6 ug vs Symbicort TBH 400/12 ug |  |
| Comparison groups   | BFF MDI 320/9.6 µg v Symbicort TBH 400/12 µg |
| Number of subjects included in analysis   | 872  |
| Analysis specification  | Pre-specified                                |
| Analysis type   | non-inferiority                              |
| Method  | mixed model for repeated measures            |
| Parameter estimate  | LS Mean Difference                           |
| Point estimate  | 0.008  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided                                      |
| lower limit   | -0.017                                       |
| upper limit   | 0.033  |

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | FEV1 AUC0-4                                  |
| Statistical analysis description:  |  |
| Primary endpoint analysis Change from baseline in FEV1 AUC0-4: BFF 160/9.6 ug vs Symbicort TBH 400/12 ug |  |
| Comparison groups  | BFF MDI 160/9.6 µg v Symbicort TBH 400/12 µg |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 854                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | non-inferiority            |
| Parameter estimate                      | LS Mean (SE)               |
| Point estimate                          | -0.007                     |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.032                     |
| upper limit                             | 0.018                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.5769                     |

**Secondary: Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI).**

|   |   |
|---|---|
| End point title   | Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI). |
| End point description:<br>Time to first moderate or severe COPD (Chronic Obstructive Pulmonary Disease) exacerbation (BFF MDI vs FF MDI). |   |
| End point type  | Secondary   |
| End point timeframe:<br>over 24 Weeks   |   |

| <b>End point values</b>     | BFF MDI<br>320/9.6 µg | BFF MDI<br>160/9.6 µg | FF MDI 9.6 µg   | BD MDI 320 µg   |
|-----------------------------|-----------------------|-----------------------|-----------------|-----------------|
| Subject group type          | Reporting group       | Reporting group       | Reporting group | Reporting group |
| Number of subjects analysed | 111                   | 127                   | 150             | 206             |
| Units: Participants         | 17                    | 20                    | 23              | 19              |

| <b>End point values</b>     | Symbicort TBH<br>400/12 µg |  |  |  |
|-----------------------------|----------------------------|--|--|--|
| Subject group type          | Reporting group            |  |  |  |
| Number of subjects analysed | 219                        |  |  |  |
| Units: Participants         | 15                         |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of subjects achieving an MCID (Minimal clinically important difference) of 4 units or more in SGRQ over 24 weeks**

|                 |  |
|-----------------|--|
| End point title | Percentage of subjects achieving an MCID (Minimal clinically |
|-----------------|--|

important difference) of 4 units or more in SGRQ over 24 weeks

End point description:

The SGRQ (St. George's Respiratory Questionnaire) is a disease-specific questionnaire, self-completed by participants, used to evaluate the effect of BFF MDI, FF MDI, BD MDI, & Symbicort TBH on health-related quality of life as compared to placebo in subjects with COPD. The scores range from 0 (minimum, best possible health status) to 100 (maximum, worst possible health status). The SGRQ contains 76 items grouped into three domains (symptoms, activity and impacts). Change from Baseline at a particular visit was calculated as the SGRQ total score at that visit minus Baseline. A decrease from baseline in SGRQ total score of 4 units or more is considered a clinically meaningful improvement in quality of life.

End point type Secondary

End point timeframe:  
over 24 weeks

| End point values              | BFF MDI<br>320/9.6 µg | BFF MDI<br>160/9.6 µg | FF MDI 9.6 µg      | BD MDI 320 µg      |
|-------------------------------|-----------------------|-----------------------|--------------------|--------------------|
| Subject group type            | Reporting group       | Reporting group       | Reporting group    | Reporting group    |
| Number of subjects analysed   | 649 <sup>[1]</sup>    | 635 <sup>[2]</sup>    | 640 <sup>[3]</sup> | 204 <sup>[4]</sup> |
| Units: Percentage of Subjects |                       |                       |                    |                    |
| Percent observed              | 47                    | 47                    | 44                 | 42                 |

Notes:

[1] - Observed % (n/N) for Treatment 302 /649

[2] - Observed % (n/N) for Treatment 299/635

[3] - Observed % (n/N) for Treatment 279/640

[4] - Observed % (n/N) for Treatment 86/204

| End point values              | Symbicort TBH<br>400/12 µg |  |  |  |
|-------------------------------|----------------------------|--|--|--|
| Subject group type            | Reporting group            |  |  |  |
| Number of subjects analysed   | 217 <sup>[5]</sup>         |  |  |  |
| Units: Percentage of Subjects |                            |  |  |  |
| Percent observed              | 48                         |  |  |  |

Notes:

[5] - Observed % (n/N) for Treatment 105/217

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in morning pre-dose trough FEV1 over 24 weeks (BFF MDI vs BD MDI)

End point title Change from baseline in morning pre-dose trough FEV1 over 24 weeks (BFF MDI vs BD MDI)

End point description:

Change from baseline in morning pre-dose trough FEV1(Forced Expiratory Volume in 1 second) over 24 weeks (BFF MDI vs BD MDI)

End point type Secondary

End point timeframe:  
over 24 weeks

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg             |
|--|------------------------|------------------------|------------------------|---------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group           |
| Number of subjects analysed                  | 627                    | 615                    | 613                    | 190                       |
| Units: Liter                                 |                        |                        |                        |                           |
| least squares mean (confidence interval 95%) | 0.058 (0.045 to 0.071) | 0.033 (0.020 to 0.047) | 0.027 (0.014 to 0.041) | -0.029 (-0.053 to -0.004) |

| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 211                        |  |  |  |
| Units: Liter                                 |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.067 (0.044 to 0.090)     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Peak change from baseline in FEV1 over 24 weeks (BFF MDI vs BD MDI)

|                 |   |
|-----------------|---|
| End point title | Peak change from baseline in FEV1 over 24 weeks (BFF MDI vs BD MDI) |
|-----------------|---|

End point description:

Peak change from baseline in FEV1 (Forced Expiratory Volume in 1 second) over 24 weeks (BFF MDI vs BD MDI)

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

End point timeframe:

over 24 weeks

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 654                    | 636                    | 643                    | 206                    |
| Units: Liter                                 |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.289 (0.276 to 0.302) | 0.274 (0.261 to 0.287) | 0.269 (0.256 to 0.282) | 0.120 (0.097 to 0.143) |

| <b>End point values</b> | Symbicort TBH<br>400/12 µg |  |  |  |
|-------------------------|----------------------------|--|--|--|
|                         |                            |  |  |  |

|  |                        |  |  |  |
|--|------------------------|--|--|--|
| Subject group type                           | Reporting group        |  |  |  |
| Number of subjects analysed                  | 218                    |  |  |  |
| Units: Liter                                 |                        |  |  |  |
| least squares mean (confidence interval 95%) | 0.281 (0.259 to 0.304) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI)

|                        |   |
|------------------------|---|
| End point title        | Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI) |
| End point description: | Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI) |
| End point type         | Secondary   |
| End point timeframe:   | over 24 Weeks   |

| End point values                             | BFF MDI 320/9.6 µg  | BFF MDI 160/9.6 µg  | FF MDI 9.6 µg       | BD MDI 320 µg       |
|--|---------------------|---------------------|---------------------|---------------------|
| Subject group type                           | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed                  | 654                 | 636                 | 641                 | 206                 |
| Units: Puffs per day                         |                     |                     |                     |                     |
| least squares mean (confidence interval 95%) | -1.3 (-1.5 to -1.1) | -1.3 (-1.4 to -1.1) | -1.1 (-1.2 to -0.9) | -0.6 (-0.9 to -0.3) |

| End point values                             | Symbicort TBH 400/12 µg |  |  |  |
|--|-------------------------|--|--|--|
| Subject group type                           | Reporting group         |  |  |  |
| Number of subjects analysed                  | 218                     |  |  |  |
| Units: Puffs per day                         |                         |  |  |  |
| least squares mean (confidence interval 95%) | -1.2 (-1.5 to -0.9)     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to onset of action on Day 1 - 5 Minutes (BFF MDI vs BD MDI)

|                 |  |
|-----------------|--|
| End point title | Time to onset of action on Day 1 - 5 Minutes (BFF MDI vs BD MDI) |
|-----------------|--|

End point description:

Time to onset of action on Day 1 (BFF MDI vs BD MDI). Change from baseline at 5 Minutes.

End point type Secondary

End point timeframe:

Day 1 - 5 Minutes

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 535                    | 536                    | 534                    | 171                    |
| Units: Liter                                 |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.157 (0.148 to 0.166) | 0.151 (0.142 to 0.161) | 0.160 (0.150 to 0.169) | 0.025 (0.009 to 0.041) |

| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 173                        |  |  |  |
| Units: Liter                                 |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.131 (0.115 to 0.148)     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to onset of action on Day 1 - 15 Minutes (BFF MDI vs BD MDI)

End point title Time to onset of action on Day 1 - 15 Minutes (BFF MDI vs BD MDI)

End point description:

Time to onset of action on Day 1- 15 Minutes (BFF MDI vs BD MDI). Change from baseline at 15 Minutes.

End point type Secondary

End point timeframe:

Day 1 - 15 Minutes

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 624                    | 615                    | 612                    | 203                    |
| Units: Liter                                 |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.190 (0.180 to 0.200) | 0.186 (0.176 to 0.196) | 0.201 (0.191 to 0.211) | 0.040 (0.022 to 0.058) |

|  |                            |  |  |  |
|--|----------------------------|--|--|--|
| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 211                        |  |  |  |
| Units: Liter                                 |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.167 (0.149 to 0.184)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to onset of action on Day 1 - 30 Minutes (BFF MDI vs BD MDI)

|                        |   |
|------------------------|---|
| End point title        | Time to onset of action on Day 1 - 30 Minutes (BFF MDI vs BD MDI)                         |
| End point description: | Time to onset of action on Day 1 (BFF MDI vs BD MDI). Change from baseline at 30 Minutes. |
| End point type         | Secondary   |
| End point timeframe:   | Day 1 - 30 Minutes  |

|  |                        |                        |                        |                        |
|--|------------------------|------------------------|------------------------|------------------------|
| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 648                    | 627                    | 638                    | 203                    |
| Units: Liter                                 |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.207 (0.196 to 0.217) | 0.207 (0.196 to 0.218) | 0.215 (0.205 to 0.226) | 0.047 (0.028 to 0.066) |

|  |                            |  |  |  |
|--|----------------------------|--|--|--|
| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 214                        |  |  |  |
| Units: Liter                                 |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.190 (0.172 to 0.209)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Time to onset of action on Day 1 - 1 Hour (BFF MDI vs BD MDI)**

---

End point title | Time to onset of action on Day 1 - 1 Hour (BFF MDI vs BD MDI)

End point description:

Time to onset of action on Day 1 (BFF MDI vs BD MDI). Change from baseline at 1 hour.

End point type | Secondary

End point timeframe:

Day 1 - 1 Hour

---

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 649                    | 628                    | 640                    | 204                    |
| Units: Liter                                 |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.225 (0.213 to 0.236) | 0.221 (0.210 to 0.233) | 0.236 (0.225 to 0.248) | 0.053 (0.033 to 0.073) |

| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 215                        |  |  |  |
| Units: Liter                                 |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.211 (0.191 to 0.231)     |  |  |  |

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Time to onset of action on Day 1 - 2 Hours (BFF MDI vs BD MDI)**

---

End point title | Time to onset of action on Day 1 - 2 Hours (BFF MDI vs BD MDI)

End point description:

Time to onset of action on Day 1 (BFF MDI vs BD MDI). Change from baseline at 2 hours.

End point type | Secondary

End point timeframe:

Day 1 - 2 Hours

---

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 649                    | 629                    | 636                    | 205                    |
| Units: Liter                                 |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.253 (0.241 to 0.265) | 0.234 (0.222 to 0.247) | 0.244 (0.231 to 0.256) | 0.063 (0.042 to 0.085) |

| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 217                        |  |  |  |
| Units: Liter                                 |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.221 (0.200 to 0.243)     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to onset of action on Day 1 - 4 Hours (BFF MDI vs BD MDI)

|                 |  |
|-----------------|--|
| End point title | Time to onset of action on Day 1 - 4 Hours (BFF MDI vs BD MDI) |
|-----------------|--|

End point description:

Time to onset of action on Day 1 (BFF MDI vs BD MDI). Change from baseline at 4 hours.

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

End point timeframe:

Day 1 - 4 Hours

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg          |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed                  | 651                    | 630                    | 634                    | 201                    |
| Units: Time Point                            |                        |                        |                        |                        |
| least squares mean (confidence interval 95%) | 0.230 (0.216 to 0.243) | 0.215 (0.202 to 0.229) | 0.212 (0.199 to 0.226) | 0.073 (0.049 to 0.097) |

| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 217                        |  |  |  |
| Units: Time Point                            |                            |  |  |  |
| least squares mean (confidence interval 95%) | 0.209 (0.186 to 0.232)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to CID (BFF MDI vs FF MDI)

End point title Time to CID (BFF MDI vs FF MDI)

End point description:

Time to Clinically Important deterioration (BFF MDI vs FF MDI).

End point type Secondary

End point timeframe:

over 24 weeks

| End point values            | BFF MDI<br>320/9.6 µg | BFF MDI<br>160/9.6 µg | FF MDI 9.6 µg      | BD MDI 320 µg     |
|-----------------------------|-----------------------|-----------------------|--------------------|-------------------|
| Subject group type          | Reporting group       | Reporting group       | Reporting group    | Reporting group   |
| Number of subjects analysed | 111 <sup>[6]</sup>    | 127 <sup>[7]</sup>    | 150 <sup>[8]</sup> | 39 <sup>[9]</sup> |
| Units: Participants         |                       |                       |                    |                   |
| number (not applicable)     | 17                    | 20                    | 23                 | 19                |

Notes:

[6] - % of subjects that had at least one COPD Exacerbation

[7] - % of subjects that had at least one COPD Exacerbation

[8] - % of subjects that had at least one COPD Exacerbation

[9] - % of subjects that had at least one COPD Exacerbation

| End point values            | Symbicort TBH<br>400/12 µg |  |  |  |
|-----------------------------|----------------------------|--|--|--|
| Subject group type          | Reporting group            |  |  |  |
| Number of subjects analysed | 32 <sup>[10]</sup>         |  |  |  |
| Units: Participants         |                            |  |  |  |
| number (not applicable)     | 15                         |  |  |  |

Notes:

[10] - % of subjects that had at least one COPD Exacerbation

## Statistical analyses

No statistical analyses for this end point

### Secondary: TDI focal score over 24 weeks

End point title TDI focal score over 24 weeks

End point description:

TDI focal score over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority).

End point type Secondary

End point timeframe:  
over 24 weeks

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg | BFF MDI<br>160/9.6 µg | FF MDI 9.6 µg       | BD MDI 320 µg       |
|--|-----------------------|-----------------------|---------------------|---------------------|
| Subject group type                           | Reporting group       | Reporting group       | Reporting group     | Reporting group     |
| Number of subjects analysed                  | 618                   | 607                   | 605                 | 185                 |
| Units: Scores on a scale                     |                       |                       |                     |                     |
| least squares mean (confidence interval 95%) | 1.12 (0.98 to 1.27)   | 1.20 (1.06 to 1.35)   | 0.98 (0.83 to 1.12) | 0.59 (0.33 to 0.86) |

| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 206                        |  |  |  |
| Units: Scores on a scale                     |                            |  |  |  |
| least squares mean (confidence interval 95%) | 1.07 (0.81 to 1.32)        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in the E-RS-Total Score over 24 weeks

End point title | Change from baseline in the E-RS-Total Score over 24 weeks

End point description:

Change from baseline in the E-RS Total Score over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, noninferiority)

End point type | Secondary

End point timeframe:  
over 24 weeks

| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg | BFF MDI<br>160/9.6 µg | FF MDI 9.6 µg       | BD MDI 320 µg       |
|--|-----------------------|-----------------------|---------------------|---------------------|
| Subject group type                           | Reporting group       | Reporting group       | Reporting group     | Reporting group     |
| Number of subjects analysed                  | 655                   | 637                   | 641                 | 206                 |
| Units: scores on a scale                     |                       |                       |                     |                     |
| least squares mean (confidence interval 95%) | -1.5 (-1.8 to -1.2)   | -1.7 (-2.0 to -1.4)   | -1.3 (-1.6 to -1.0) | -0.9 (-1.4 to -0.3) |

|  |                            |  |  |  |
|--|----------------------------|--|--|--|
| <b>End point values</b>                      | Symbicort TBH<br>400/12 µg |  |  |  |
| Subject group type                           | Reporting group            |  |  |  |
| Number of subjects analysed                  | 218                        |  |  |  |
| Units: scores on a scale                     |                            |  |  |  |
| least squares mean (confidence interval 95%) | -1.4 (-1.9 to -0.9)        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Substudy: 12-hour PFT endpoint FEV1 AUC0-12

|                 |   |
|-----------------|---|
| End point title | Substudy: 12-hour PFT endpoint FEV1 AUC0-12 <sup>[11]</sup> |
|-----------------|---|

End point description:

Substudy: 12-hour PFT (Pulmonary Function Test) endpoint FEV1 (Forced Expiratory Volume) AUC0-12 (Area under the Curve 0-12)

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

at Week 12

Notes:

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

Justification: The subjects on Symbicort TBH 400ug Arm, did not participate in the Sub-Study

|  |                        |                        |                        |                         |
|--|------------------------|------------------------|------------------------|-------------------------|
| <b>End point values</b>                      | BFF MDI<br>320/9.6 µg  | BFF MDI<br>160/9.6 µg  | FF MDI 9.6 µg          | BD MDI 320 µg           |
| Subject group type                           | Reporting group        | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed                  | 160                    | 167                    | 162                    | 47                      |
| Units: Liter                                 |                        |                        |                        |                         |
| least squares mean (confidence interval 95%) | 0.135 (0.107 to 0.163) | 0.124 (0.097 to 0.152) | 0.117 (0.089 to 0.145) | 0.024 (-0.028 to 0.075) |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Serious Adverse Events were collected from the time the subject signed informed consent throughout the treatment period and up to approximately 30 weeks, which includes screening and follow up (14 days after last dose of study drug).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Budesonide Formoterol Fumarate Metered Dose Inhalation 320/9.6 µg

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

Reporting group description:

Budesonide Formoterol Fumarate Metered Dose Inhalation 160/9.6 µg

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

Reporting group description:

Formoterol Fumarate Metered Dose Inhalation 9.6 µg

|                       |               |
|-----------------------|---------------|
| Reporting group title | BD MDI 320 µg |
|-----------------------|---------------|

Reporting group description:

Budesonide Metered Dose Inhalation 320 µg

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Symbicort TBH 400/12 µg |
|-----------------------|-------------------------|

Reporting group description:

Symbicort Turbuhaler 400/12 µg

| Serious adverse events  | BFF MDI 320/9.6 µg | BFF MDI 160/9.6 µg | FF MDI 9.6 µg     |
|---|--------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events                   |                    |                    |                   |
| subjects affected / exposed   | 42 / 655 (6.41%)   | 45 / 637 (7.06%)   | 72 / 644 (11.18%) |
| number of deaths (all causes)                                       | 3                  | 2                  | 2                 |
| number of deaths resulting from adverse events                      | 0                  | 0                  | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                   |
| Adenocarcinoma of colon   |                    |                    |                   |
| subjects affected / exposed   | 0 / 655 (0.00%)    | 0 / 637 (0.00%)    | 0 / 644 (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             |
| Brain cancer metastatic   |                    |                    |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Breast cancer male</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Bronchial carcinoma</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Gastric neoplasm</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Lung neoplasm malignant</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Mesothelioma</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Metastases to liver</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Metastatic carcinoma of the bladder</b>      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Non-small cell lung cancer</b>               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Pancreatic carcinoma metastatic</b>          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Prostate cancer</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Transitional cell carcinoma</b>              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Vascular disorders</b>                       |                 |                 |                 |
| <b>Arteriosclerosis</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Haematoma</b>                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypertensive emergency</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Peripheral artery thrombosis</b>             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Peripheral ischaemia</b>                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                                 | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombophlebitis superficial                                |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>General disorders and administration site conditions</b> |                 |                 |                 |
| Chest discomfort  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Chest pain  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Death   |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Incarcerated hernia   |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden cardiac death  |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Reproductive system and breast disorders</b>             |                 |                 |                 |
| Prostatic haemorrhage                                       |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Respiratory, thoracic and mediastinal disorders |                  |                  |                  |
| Chronic obstructive pulmonary disease           |                  |                  |                  |
| subjects affected / exposed                     | 15 / 655 (2.29%) | 10 / 637 (1.57%) | 29 / 644 (4.50%) |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 10           | 0 / 35           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Acute respiratory failure                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 655 (0.31%)  | 2 / 637 (0.31%)  | 4 / 644 (0.62%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pulmonary embolism                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 655 (0.15%)  | 0 / 637 (0.00%)  | 1 / 644 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Respiratory failure                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 655 (0.00%)  | 0 / 637 (0.00%)  | 1 / 644 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pleural effusion                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 655 (0.00%)  | 0 / 637 (0.00%)  | 1 / 644 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Psychiatric disorders                           |                  |                  |                  |
| Mental status changes                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 655 (0.00%)  | 1 / 637 (0.16%)  | 0 / 644 (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            |
| Product issues                                  |                  |                  |                  |
| Device battery issue                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 655 (0.00%)  | 0 / 637 (0.00%)  | 1 / 644 (0.16%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Injury, poisoning and procedural complications  |                  |                  |                  |
| Hip fracture                                    |                  |                  |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| Acetabulum fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Dural tear                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Forearm fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Radius fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Thermal burn                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Upper limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular pseudoaneurysm                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Skull fractured base                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 5 / 637 (0.78%) | 2 / 644 (0.31%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 1 / 637 (0.16%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 2 / 637 (0.31%) | 2 / 644 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 2 / 637 (0.31%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 2 / 637 (0.31%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Atrial flutter</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cardiac failure</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 655 (0.31%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cardiac failure chronic</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 2 / 637 (0.31%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Myocardial ischaemia</b>                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Atrioventricular block complete</b>          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Cardiac arrest</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Coronary artery disease</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Arteriosclerosis coronary artery</b>         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Congestive cardiomyopathy</b>                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Coronary artery stenosis</b>                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Myocardial infarction</b>                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Nervous system disorders</b>                 |                 |                 |                 |
| <b>Ischaemic stroke</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 2 / 644 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cerebrovascular accident</b>                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Transient ischaemic attack</b>               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Carotid artery stenosis</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Embolic stroke</b>                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Epilepsy</b>                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Hypoaesthesia</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Intracranial aneurysm</b>                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Syncope</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Eye disorders</b>                            |                 |                 |                 |
| <b>Cataract</b>                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastrointestinal disorders</b>               |                 |                 |                 |
| <b>Small intestinal obstruction</b>             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 2 / 644 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Pancreatitis acute</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Abdominal pain</b>                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulum intestinal                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal ulcer                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hiatus hernia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Inflammatory bowel disease                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| Strangulated umbilical hernia                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bile duct stone                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Chronic kidney disease                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertonic bladder                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal tubular necrosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal cyst                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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 |                 |                 |                 |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bursitis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Musculoskeletal chest pain                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Tendonitis                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Infections and infestations</b>              |                 |                 |                 |
| <b>Pneumonia</b>                                |                 |                 |                 |
| subjects affected / exposed                     | 4 / 655 (0.61%) | 5 / 637 (0.78%) | 6 / 644 (0.93%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 5           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Abdominal hernia gangrenous</b>              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Breast abscess</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cellulitis</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Clostridium difficile colitis</b>            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Sepsis</b>                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| <b>Staphylococcal infection</b>                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Tooth abscess</b>                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 655 (0.00%) | 1 / 637 (0.16%) | 0 / 644 (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           |
| <b>Metabolism and nutrition disorders</b>       |                 |                 |                 |
| Cachexia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Diabetes mellitus                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetes with hyperosmolarity                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 655 (0.15%) | 0 / 637 (0.00%) | 0 / 644 (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           |
| Electrolyte imbalance                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gout  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 655 (0.00%) | 0 / 637 (0.00%) | 1 / 644 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>  | BD MDI 320 µg    | Symbicort TBH 400/12 µg |  |
|--|------------------|-------------------------|--|
| <b>Total subjects affected by serious adverse events</b>                   |                  |                         |  |
| subjects affected / exposed  | 15 / 206 (7.28%) | 20 / 219 (9.13%)        |  |
| number of deaths (all causes)  | 0                | 2                       |  |
| number of deaths resulting from adverse events                             | 0                | 0                       |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                  |                         |  |
| Adenocarcinoma of colon  |                  |                         |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Brain cancer metastatic</b>                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Breast cancer male</b>                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bronchial carcinoma</b>                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastric neoplasm</b>                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Lung neoplasm malignant</b>                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Mesothelioma</b>                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Metastases to liver</b>                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Metastatic carcinoma of the bladder</b>      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Non-small cell lung cancer</b>               |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Pancreatic carcinoma metastatic</b>          |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Prostate cancer</b>                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Transitional cell carcinoma</b>              |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Vascular disorders</b>                       |                 |                 |  |
| <b>Arteriosclerosis</b>                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Haematoma</b>                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypertensive emergency</b>                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Peripheral artery thrombosis</b>             |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral ischaemia                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis superficial                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest discomfort                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Incarcerated hernia                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Sudden cardiac death                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Prostatic haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 2 / 206 (0.97%) | 6 / 219 (2.74%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device battery issue                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                           | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Injury, poisoning and procedural complications</b> |                 |                 |  |
| <b>Hip fracture</b>                                   |                 |                 |  |
| subjects affected / exposed                           | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Acetabulum fracture</b>                            |                 |                 |  |
| subjects affected / exposed                           | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Dural tear</b>                                     |                 |                 |  |
| subjects affected / exposed                           | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Femur fracture</b>                                 |                 |                 |  |
| subjects affected / exposed                           | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Forearm fracture</b>                               |                 |                 |  |
| subjects affected / exposed                           | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Lower limb fracture</b>                            |                 |                 |  |
| subjects affected / exposed                           | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Radius fracture</b>                                |                 |                 |  |
| subjects affected / exposed                           | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Rib fracture</b>                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Thermal burn</b>                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Upper limb fracture</b>                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Vascular pseudoaneurysm</b>                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Skull fractured base</b>                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Cardiac disorders</b>                        |                 |                 |  |
| <b>Atrial fibrillation</b>                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Cardiac failure congestive</b>               |                 |                 |  |
| subjects affected / exposed                     | 2 / 206 (0.97%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Acute myocardial infarction</b>              |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Angina pectoris</b>                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure chronic                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block complete                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriosclerosis coronary artery                |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congestive cardiomyopathy                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery stenosis                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Embolitic stroke</b>                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Epilepsy</b>                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypoaesthesia</b>                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Intracranial aneurysm</b>                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Syncope</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Eye disorders</b>                            |                 |                 |  |
| <b>Cataract</b>                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |
| <b>Small intestinal obstruction</b>             |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Pancreatitis acute</b>                       |                 |                 |  |

|   |                 |                 |
|---|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 2 / 219 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Abdominal pain</b>                           |                 |                 |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Colitis ischaemic</b>                        |                 |                 |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Diverticulum intestinal</b>                  |                 |                 |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Gastrointestinal ulcer</b>                   |                 |                 |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Hiatus hernia</b>                            |                 |                 |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Inflammatory bowel disease</b>               |                 |                 |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Inguinal hernia</b>                          |                 |                 |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |
| <b>Pancreatitis</b>                             |                 |                 |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Strangulated umbilical hernia</b>            |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Upper gastrointestinal haemorrhage</b>       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hepatobiliary disorders</b>                  |                 |                 |  |
| <b>Cholecystitis</b>                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bile duct stone</b>                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Cholelithiasis</b>                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Cholecystitis acute</b>                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Renal and urinary disorders</b>              |                 |                 |  |
| <b>Acute kidney injury</b>                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Chronic kidney disease</b>                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertonic bladder                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cyst                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bursitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal chest pain                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Tendonitis</b>                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Infections and infestations</b>              |                 |                 |  |
| <b>Pneumonia</b>                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 3 / 219 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Abdominal hernia gangrenous</b>              |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Breast abscess</b>                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Cellulitis</b>                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Clostridium difficile colitis</b>            |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Sepsis</b>                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Staphylococcal infection</b>                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Cachexia  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 219 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes with hyperosmolarity                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Electrolyte imbalance                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gout  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 0 / 219 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>   | BFF MDI 320/9.6 µg   | BFF MDI 160/9.6 µg   | FF MDI 9.6 µg  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 240 / 655 (36.64%)   | 201 / 637 (31.55%)   | 219 / 644 (34.01%)   |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 14 / 655 (2.14%)<br>14   | 22 / 637 (3.45%)<br>22   | 15 / 644 (2.33%)<br>15   |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)  | 19 / 655 (2.90%)<br>27   | 8 / 637 (1.26%)<br>10  | 15 / 644 (2.33%)<br>15   |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 1 / 655 (0.15%)<br>1   | 1 / 637 (0.16%)<br>1   | 5 / 644 (0.78%)<br>5   |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 9 / 655 (1.37%)<br>9   | 9 / 637 (1.41%)<br>9   | 9 / 644 (1.40%)<br>9   |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dysphonia<br>subjects affected / exposed<br>occurrences (all) | 7 / 655 (1.07%)<br>8<br><br>12 / 655 (1.83%)<br>12<br><br>16 / 655 (2.44%)<br>16 | 15 / 637 (2.35%)<br>15<br><br>11 / 637 (1.73%)<br>11<br><br>13 / 637 (2.04%)<br>13 | 15 / 644 (2.33%)<br>15<br><br>9 / 644 (1.40%)<br>9<br><br>3 / 644 (0.47%)<br>3 |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)  | 6 / 655 (0.92%)<br>6   | 2 / 637 (0.31%)<br>2   | 4 / 644 (0.62%)<br>4   |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 18 / 655 (2.75%)<br>21   | 13 / 637 (2.04%)<br>14   | 18 / 644 (2.80%)<br>19   |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                         | 14 / 655 (2.14%)<br>15 | 6 / 637 (0.94%)<br>6   | 6 / 644 (0.93%)<br>7   |
| <b>Infections and infestations</b>  |                        |                        |                        |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 40 / 655 (6.11%)<br>46 | 40 / 637 (6.28%)<br>44 | 43 / 644 (6.68%)<br>46 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)     | 25 / 655 (3.82%)<br>27 | 21 / 637 (3.30%)<br>24 | 20 / 644 (3.11%)<br>20 |
| Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences (all) | 16 / 655 (2.44%)<br>17 | 10 / 637 (1.57%)<br>10 | 30 / 644 (4.66%)<br>36 |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)                      | 17 / 655 (2.60%)<br>18 | 14 / 637 (2.20%)<br>15 | 5 / 644 (0.78%)<br>6   |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                            | 16 / 655 (2.44%)<br>17 | 7 / 637 (1.10%)<br>8   | 10 / 644 (1.55%)<br>10 |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                             | 10 / 655 (1.53%)<br>12 | 9 / 637 (1.41%)<br>10  | 12 / 644 (1.86%)<br>13 |

| <b>Non-serious adverse events</b>  | BD MDI 320 µg        | Symbicort TBH 400/12 µg |  |
|--|----------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 75 / 206 (36.41%)    | 57 / 219 (26.03%)       |  |
| <b>Vascular disorders</b>  |                      |                         |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                     | 5 / 206 (2.43%)<br>5 | 4 / 219 (1.83%)<br>5    |  |
| <b>Nervous system disorders</b>  |                      |                         |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 206 (1.46%)<br>4 | 1 / 219 (0.46%)<br>3    |  |
| <b>General disorders and administration site conditions</b>                          |                      |                         |  |

|   |  |  |  |
|---|--|--|--|
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 5 / 206 (2.43%)<br>5   | 1 / 219 (0.46%)<br>1   |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 5 / 206 (2.43%)<br>6   | 3 / 219 (1.37%)<br>3   |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dysphonia<br>subjects affected / exposed<br>occurrences (all) | 7 / 206 (3.40%)<br>7<br><br>7 / 206 (3.40%)<br>7<br><br>2 / 206 (0.97%)<br>2 | 0 / 219 (0.00%)<br>0<br><br>3 / 219 (1.37%)<br>3<br><br>1 / 219 (0.46%)<br>1 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)  | 5 / 206 (2.43%)<br>5   | 1 / 219 (0.46%)<br>1   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 3 / 206 (1.46%)<br>3<br><br>0 / 206 (0.00%)<br>0                             | 2 / 219 (0.91%)<br>2<br><br>8 / 219 (3.65%)<br>8                             |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Chronic obstructive pulmonary disease          | 17 / 206 (8.25%)<br>18<br><br>5 / 206 (2.43%)<br>7                           | 14 / 219 (6.39%)<br>18<br><br>3 / 219 (1.37%)<br>3                           |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                     | 2 / 206 (0.97%)<br>2 | 6 / 219 (2.74%)<br>6 |  |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all) | 3 / 206 (1.46%)<br>3 | 3 / 219 (1.37%)<br>3 |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)       | 4 / 206 (1.94%)<br>4 | 2 / 219 (0.91%)<br>2 |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)        | 2 / 206 (0.97%)<br>2 | 5 / 219 (2.28%)<br>5 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 01 July 2016    | Clarified dose of open label Symbicort® TBH Updated synopsis, Safety endpoints, Inclusion/Exclusion Criteria. |
| 24 October 2017 | Updated Protocol objective, updated endpoints, clarification of statistical methods.                          |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported