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 ≤ 10 puffs remaining, and o Their next scheduled study clinic visit is not the following day

Arms

Are arms mutually exclusive?	Yes
Arm title	BFF MDI 320/9.6 µg

Arm description:

Budesonide Formoterol Fumarate Metered Dose Inhalation 320/9.6 µg

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

Arm title	BFF MDI 160/9.6 µg

Arm description:

Budesonide Formoterol Fumarate Metered Dose Inhalation 160/9.6 µg

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

Arm title	FF MDI 9.6 µg

Arm description:

Formoterol Fumarate Metered Dose Inhalation 9.6 µg

Arm type	Experimental

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

Dosage and administration details:
Taken as 2 inhalations BID

Arm title	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

Arm title	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

Number of subjects in period 1	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

Number of subjects in period 1	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: 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	

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

Reporting group values	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	

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	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)

End point values	Symbicort TBH 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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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	

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	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)

End point values	Symbicort TBH 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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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:

Time to first moderate or severe COPD (Chronic Obstructive Pulmonary Disease) exacerbation (BFF MDI vs FF 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	111	127	150	206
Units: Participants	17	20	23	19

End point values	Symbicort TBH 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 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	649[1]	635[2]	640[3]	204[4]
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 400/12 µg			
Subject group type	Reporting group			
Number of subjects analysed	217[5]			
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

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	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)

End point values	Symbicort TBH 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

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	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)

End point values	Symbicort TBH 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	

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	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)

End point values	Symbicort TBH 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	

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	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)

End point values	Symbicort TBH 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

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	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)

End point values	Symbicort TBH 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

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

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	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)

End point values	Symbicort TBH 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

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	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)

End point values	Symbicort TBH 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

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	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)

End point values	Symbicort TBH 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 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	111[6]	127[7]	150[8]	39[9]
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 400/12 µg			
Subject group type	Reporting group			
Number of subjects analysed	32[10]			
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

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	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)

End point values	Symbicort TBH 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

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	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)

End point values	Symbicort TBH 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[11]

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

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	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
Breast cancer male			
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
Bronchial carcinoma			
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
Gastric neoplasm			
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
Lung neoplasm malignant			
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
Mesothelioma			
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
Metastases to liver			
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
Metastatic carcinoma of the bladder			
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
Non-small cell lung cancer			

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
Pancreatic carcinoma metastatic			
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
Prostate cancer			
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
Transitional cell carcinoma			
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
Vascular disorders			
Arteriosclerosis			
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
Haematoma			
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
Hypertensive emergency			
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
Peripheral artery thrombosis			
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
Peripheral ischaemia			

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
General disorders and administration site conditions			
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
Reproductive system and breast disorders			
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
Atrial flutter			
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
Cardiac failure			
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
Cardiac failure chronic			
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
Myocardial ischaemia			
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
Atrioventricular block complete			
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
Cardiac arrest			
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
Coronary artery disease			
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
Arteriosclerosis coronary artery			

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
Congestive cardiomyopathy			
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
Coronary artery stenosis			
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
Myocardial infarction			
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
Nervous system disorders			
Ischaemic stroke			
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
Cerebrovascular accident			
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
Transient ischaemic attack			
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
Carotid artery stenosis			
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
Embolic stroke			

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
Epilepsy			
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
Hypoaesthesia			
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
Intracranial aneurysm			
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
Syncope			
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
Eye disorders			
Cataract			
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
Gastrointestinal disorders			
Small intestinal obstruction			
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
Pancreatitis acute			
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
Abdominal 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
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
Infections and infestations			
Pneumonia			
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
Abdominal hernia gangrenous			
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
Breast abscess			
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
Cellulitis			
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
Clostridium difficile colitis			
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
Sepsis			
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
Staphylococcal infection			
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
Tooth abscess			

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
Metabolism and nutrition disorders			
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

Serious adverse events	BD MDI 320 µg	Symbicort TBH 400/12 µg	
Total subjects affected by serious adverse events			
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	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
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	
Brain cancer metastatic			
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	
Breast cancer male			
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	
Bronchial carcinoma			
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	
Gastric neoplasm			
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	
Lung neoplasm malignant			
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	
Mesothelioma			
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	
Metastases to liver			
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	
Metastatic carcinoma of the 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	
Non-small cell lung cancer			
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	
Pancreatic carcinoma metastatic			
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	
Prostate cancer			
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	
Transitional cell carcinoma			
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	
Vascular disorders			
Arteriosclerosis			
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	
Haematoma			
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	
Hypertensive emergency			
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 artery thrombosis			

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	
Injury, poisoning and procedural complications			
Hip fracture			
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	
Acetabulum fracture			
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	
Dural tear			
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	
Femur fracture			
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	
Forearm fracture			
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	
Lower limb fracture			
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	
Radius fracture			
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	
Rib fracture			

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	
Thermal burn			
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	
Upper limb fracture			
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	
Vascular pseudoaneurysm			
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	
Skull fractured base			
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 disorders			
Atrial fibrillation			
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 congestive			
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	
Acute myocardial infarction			
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 pectoris			

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	
Embolic stroke			
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	
Epilepsy			
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	
Hypoaesthesia			
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	
Intracranial aneurysm			
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	
Syncope			
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	
Eye disorders			
Cataract			
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	
Gastrointestinal disorders			
Small intestinal obstruction			
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	
Pancreatitis acute			

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	
Abdominal 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	
Colitis ischaemic			
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	
Diverticulum intestinal			
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	
Gastrointestinal ulcer			
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	
Hiatus 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	
Inflammatory bowel 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	
Inguinal hernia			
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	
Pancreatitis			

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	
Strangulated umbilical hernia			
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	
Upper gastrointestinal 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	
Hepatobiliary disorders			
Cholecystitis			
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	
Bile duct stone			
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	
Cholelithiasis			
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	
Cholecystitis acute			
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 and urinary disorders			
Acute kidney injury			
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	
Chronic kidney 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	
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	
Tendonitis			
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	
Infections and infestations			
Pneumonia			
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	
Abdominal hernia gangrenous			
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	
Breast 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	
Cellulitis			
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	
Clostridium difficile colitis			
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	
Sepsis			
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	
Staphylococcal infection			

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 %

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

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

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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported