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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	PT003014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pearl Therapeutics Inc.
Sponsor organisation address	200 Cardinal Way, Redwood City, United States, 94063
Public contact	Colin Reisner, Pearl Therapeutics Inc., 1 6503052600, creisner@pearltherapeutics.com
Scientific contact	Colin Reisner, Pearl Therapeutics Inc., 1 6503052600, creisner@pearltherapeutics.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

For subjects who were on ICS LABA, the ICS LABA was discontinued, however, then prescribed an ICS Monotherapy at an equivalent dosing regimen for the duration of the study.
Subjects were also given sponsor provided Ventolin HFA as rescue medication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	868
From 65 to 84 years	872
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GFF MDI 14.4/9.6 ug

Arm description:

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

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

Dosage and administration details:

Taken as 2 Inhalations BID

Arm title	FF MDI 9.6 ug

Arm description:

Formoterol Fumarate, Metered Dose Inhalation 9.6 ug

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

Dosage and administration details:

Taken as 2 inhalations BID

Arm title	GP MDI 14.4 ug

Arm description:

Glycopyrronium 14.4 ug Metered Dose Inhalation

Arm type	Experimental

Investigational medicinal product name	Glycopyrronium MDI
Investigational medicinal product code	
Other name	GP MDI
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:
Taken as 2 inhalations BID

Arm title	Placebo MDI

Arm description:
Placebo Metered Dose Inhalation

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

Dosage and administration details:
Taken as 2 inhalations BID

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

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

Baseline characteristics

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

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

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

End points

End points reporting groups	
Reporting group title	GFF MDI 14.4/9.6 ug
Reporting group description: Glycopyrronium, Formoterol Fumarate, Metered Dose Inhalation 14.4/9.6 ug	
Reporting group title	FF MDI 9.6 ug
Reporting group description: Formoterol Fumarate, Metered Dose Inhalation 9.6 ug	
Reporting group title	GP MDI 14.4 ug
Reporting group description: Glycopyrronium 14.4 ug Metered Dose Inhalation	
Reporting group title	Placebo MDI
Reporting group description: Placebo Metered Dose Inhalation	

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

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

Statistical analyses

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

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

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

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

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

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

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

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

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

Statistical analyses

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

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

Statistical analysis title	Change from baseline in AM pre-dose trough FEV1
Statistical analysis description:	
Change from baseline in morning pre-dose trough FEV1 over weeks 12-24, Japan approach	

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

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

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

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

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

Statistical analyses

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

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

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

Statistical analysis title	Change from baseline in AM pre-dose trough FEV1
Statistical analysis description:	
Change from baseline in morning pre-dose trough FEV1 (Liters) over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach.	
Comparison groups	GP MDI 14.4 ug v Placebo MDI
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.073
upper limit	0.125

Statistical analysis title	Change from baseline in AM pre-dose trough FEV1
Statistical analysis description:	
Change from baseline in morning pre-dose trough FEV1 (Liters) over 24 weeks. Primary endpoint, EU/SK/TW approach, Secondary endpoint US/China approach.	
Comparison groups	GFF MDI 14.4/9.6 ug v FF MDI 9.6 ug
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.052
upper limit	0.092

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

	Symptomatic Population
End point description:	
TDI Focal Score – Secondary Endpoint, Japan approach	
End point type	Secondary
End point timeframe:	
over weeks 12-24	

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Peak change from baseline in FEV1 within 2 hours post-dosing at Week 24 US/China approach
End point description:	
Peak change from baseline in FEV1 within 2 hours post-dosing at Week 24 US/China approach	
End point type	Secondary
End point timeframe:	
at week 24	

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Peak change from baseline in FEV1 within 2 hours post-dosing over weeks 12-24 Japan approach

End point description:

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

End point type	Secondary

End point timeframe:

over weeks 12-24

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

over 24 weeks

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

at week 24

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

over weeks 12-24

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

over 24 weeks

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Day 1

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Time to onset of action on Day 1 - 15 Minutes Post-Dose, all approaches

End point description:

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

End point type	Secondary

End point timeframe:

Day 1

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time the subject signed consent throughout the four treatment periods of 24 weeks and up to 10 days following the last dose of study drug.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	GFF MDI 14.4/9.6 ug

Reporting group description:

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

Reporting group title	FF MDI 9.6 ug

Reporting group description:

Formoterol Fumarate, Metered Dose Inhalation 9.6 ug

Reporting group title	GP MDI 14.4 ug

Reporting group description:

Glycopyrronium 14.4 ug Metered Dose Inhalation

Reporting group title	Placebo MDI

Reporting group description:

Placebo Metered Dose Inhalation

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

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

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

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

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

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

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

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

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

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

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

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

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

Serious adverse events	Placebo MDI		

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported