Clinical trial results:
A randomised, double-blind, double dummy, parallel group study comparing Fluticasone propionate / formoterol fumarate (flutiform®) 250/10 g (2 puffs BID) and flutiform® 125/5 g (2 puffs BID) versus Formoterol fumarate dihydrate (Atimos®) 12 g (1 puff BID) in subjects with chronic obstructive pulmonary disease (COPD).

Summary

EudraCT number	2012-004162-17
Trial protocol	DE GB HU LV LT BG ES CZ SK
Global end of trial date	04 May 2016

Results information

Result version number	v1 (current)
This version publication date	19 May 2017
First version publication date	19 May 2017

Trial information

Trial identification

Sponsor protocol code	FLT3509

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01946620
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Ltd.
Sponsor organisation address	194-198 Cambridge Science Park, Cambridge, United Kingdom, CB4 0GW
Public contact	European Medical Operations, Mundipharma Research Limited, +44 1223 424900 , info@contact-clinical-trials.com
Scientific contact	European Medical Operations, Mundipharma Research Limited, +44 1223 424900 , info@contact-clinical-trials.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2016
Global end of trial reached?	Yes
Global end of trial date	04 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Show superiority in the efficacy of flutiform 250/10 µg (2 puffs bid) compared with formoterol 12 µg (1 puff bid) based on the annual rate of moderate and severe COPD exacerbations during the 52-week treatment period.

Protection of trial subjects:

The population that was enrolled was selected on the basis of multiple prior trials which have demonstrated the benefits of ICS-LABA treatment in this target group. In order to reduce risks of participation in a 12-month study subjects were asked to complete an electronic diary, the EXACT-PRO, on a daily basis. This tool has been rigorously developed and has undergone extensive validation. This questionnaire took about 5 minutes to complete. If a subject's score increased by ≥ 9 points for 3 consecutive days, or ≥ 12 points for 2 consecutive days, compared to baseline, which were validated "exacerbation" thresholds, an alert was sent to both the subject and the Investigator to trigger patient-physician contact to determine whether the subject needed to attend clinic for an unscheduled visit to have their symptoms reviewed. This process provided a robust safety net in excess of that used in the vast majority of previous COPD studies.

Background therapy:

Subjects entered a 2-week, open-label, run-in phase during which they ceased their current maintenance treatment and commenced tiotropium (Spiriva® Handihaler®). The run-in phase was intended to ensure a standardised baseline in all subjects such that changes from baseline represented the same change in all patients. Tiotropium was selected as run-in therapy in order to avoid selection bias (or enrichment) during the run-in period which might favour either of the study treatments to which patients are subsequently randomised. Tiotropium is also recommended therapy for category C and D patients and as such is appropriate. Salbutamol 100 µg was used as rescue medication in the run-in and treatment period.

Evidence for comparator:

The active components of flutiform are the inhaled glucocorticosteroid (ICS) fluticasone-17-propionate and the inhaled long acting β2-agonist (LABA) formoterol fumarate. Both have both been on the market for many years, and the safety and tolerability of both have been extensively documented in the literature Given the literature, it was expected that both fluticasone doses of 250 and 500 ug BID within flutiform would confer incremental benefit over formoterol monotherapy, whilst also allowing the potential approval of a fluticasone dose half that previously approved as being safe and effective for COPD in the EU.

Actual start date of recruitment	15 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 272
Country: Number of subjects enrolled	Romania: 92
Country: Number of subjects enrolled	Russian Federation: 66

Country: Number of subjects enrolled	South Africa: 158
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Ukraine: 137
Country: Number of subjects enrolled	Poland: 229
Country: Number of subjects enrolled	Slovakia: 50
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 53
Country: Number of subjects enrolled	Bulgaria: 155
Country: Number of subjects enrolled	Czech Republic: 53
Country: Number of subjects enrolled	Germany: 215
Country: Number of subjects enrolled	Hungary: 191
Country: Number of subjects enrolled	Latvia: 57
Country: Number of subjects enrolled	Lithuania: 8
Worldwide total number of subjects	1765
EEA total number of subjects	1114

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)	970
From 65 to 84 years	790
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

1765 subjects were enrolled across 223 sites in 16 different countries between October 2013 and March 2015.

Pre-assignment

Screening details:

A total of 2328 subjects provided written informed consent and were screened; 1870 subjects entered the run-in and 1765 subjects were randomised and treated. 458 subjects failed screening; 401 subjects due to failed screening procedures, 46 subjects withdrew, 7 subjects failed due to administrative reasons, 2 subjects failed due to adverse events.

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, Data analyst, Assessor

Blinding implementation details:

The randomisation schedule was filed securely by the Sponsor/IRT provider in a manner such that blinding was properly maintained throughout the study. Medication codes were not available until the completion of the study and until after clinical data base lock, except in the case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Flutiform High Dose

Arm description:

Flutiform 250/10 µg (2 puffs BID)

Arm type	Experimental
Investigational medicinal product name	Flutiform
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

250/10 µg, 2 puffs, Q12h

Arm title	Flutiform Medium Dose

Arm description:

Flutiform 125/5 µg (2 puffs BID)

Arm type	Experimental
Investigational medicinal product name	Flutiform
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

125/5 µg, 2 puffs, Q12h

Arm title	Formoterol

Arm description:

Formoterol 12 µg (1 puff BID)

Arm type	Active comparator

Investigational medicinal product name	Formoterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

12 µg, 1 pufs, Q12h

Number of subjects in period 1	Flutiform High Dose	Flutiform Medium Dose	Formoterol
Started	587	588	590
Completed	466	447	436
Not completed	121	141	154
Consent withdrawn by subject	60	68	81
Non-compliance with Study Drug	-	2	4
Administrative	-	3	1
Adverse event, non-fatal	29	40	34
Lost to follow-up	3	4	2
Lack of efficacy	18	15	18
Protocol deviation	11	9	14

Baseline characteristics

Reporting groups	
Reporting group title	Flutiform High Dose
Reporting group description:	
Flutiform 250/10 µg (2 puffs BID)	
Reporting group title	Flutiform Medium Dose
Reporting group description:	
Flutiform 125/5 µg (2 puffs BID)	
Reporting group title	Formoterol
Reporting group description:	
Formoterol 12 µg (1 puff BID)	

Reporting group values	Flutiform High Dose	Flutiform Medium Dose	Formoterol
Number of subjects	587	588	590
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)	326	346	298
Adults (65 years and over)	261	242	292
Age continuous			
Units: years			
arithmetic mean	63.8	63	64
standard deviation	± 7.92	± 7.81	± 7.87
Gender categorical			
Units: Subjects			
Female	144	161	142
Male	443	427	448
Race			
Units: Subjects			
Caucasian	576	564	573
Black	3	7	2
Asian	3	11	11
Oriental	0	0	0
Other	5	6	4
Weight			
Units: kg			
arithmetic mean	74.84	75.29	75.71
standard deviation	± 17.04	± 17.19	± 16.837
Height			
Units: cm			
arithmetic mean	170.4	170.1	170.7

standard deviation	± 8.63	± 8.43	± 8.44
BMI			
Units: kg/m²			
arithmetic mean	25.684	25.92	25.923
standard deviation	± 4.9882	± 5.2721	± 5.1811

Reporting group values	Total		
Number of subjects	1765		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	970		
Adults (65 years and over)	795		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	447		
Male	1318		
Race			
Units: Subjects			
Caucasian	1713		
Black	12		
Asian	25		
Oriental	0		
Other	15		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
BMI			
Units: kg/m²			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Flutiform High Dose
Reporting group description: Flutiform 250/10 µg (2 puffs BID)	
Reporting group title	Flutiform Medium Dose
Reporting group description: Flutiform 125/5 µg (2 puffs BID)	
Reporting group title	Formoterol
Reporting group description: Formoterol 12 µg (1 puff BID)	

Primary: Annualised rate of moderate and severe COPD exacerbations during the 52-week treatment period

End point title	Annualised rate of moderate and severe COPD exacerbations during the 52-week treatment period

End point description:

The primary efficacy endpoint was the annualised rate of moderate and severe COPD exacerbations during the 52-week treatment period (based on medical intervention), which was analysed with a negative binomial regression model to estimate rate ratios and corresponding 95% confidence intervals (CIs).

End point type	Primary

End point timeframe:

Over the 52 week treatment period, from baseline to week 52.

End point values	Flutiform High Dose	Flutiform Medium Dose	Formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	587	588	590	
Units: Rate of exacerbations				
number (confidence interval 95%)	0.81 (0.69 to 0.96)	0.81 (0.69 to 0.96)	0.87 (0.73 to 1.03)	

Statistical analyses

Statistical analysis title	Superiority of Flutiform High Dose vs Formoterol

Statistical analysis description:

For the primary comparison of interest, the null hypothesis was that the rate ratio between the flutiform high dose treatment group and the formoterol treatment group is equal to 1. The alternative hypothesis was that the rate ratio between the flutiform high dose treatment group and the formoterol treatment group is not equal to 1.

Comparison groups	Flutiform High Dose v Formoterol

Number of subjects included in analysis	1177
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.401
Method	Negative Binomial Regression
Parameter estimate	Rate ratio (test/reference)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.1

Notes:

[1] - Superiority was only concluded if the 95% CI for the rate ratio lay entirely below 1.

Statistical analysis title	Superiority of Flutiform Medium Dose vs Formoterol
Comparison groups	Flutiform Medium Dose v Formoterol
Number of subjects included in analysis	1178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.402
Method	Negative Binomial Regression
Parameter estimate	Rate ratio (test/reference)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.1

Statistical analysis title	Superiority of Flutiform High and Medium Doses
Comparison groups	Flutiform High Dose v Flutiform Medium Dose
Number of subjects included in analysis	1175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.996
Method	Negative Binomial Regression
Parameter estimate	Rate ratio (test/reference)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.18

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the point at which the Informed Consent was signed until 7 days after the subject left the study. This included new AEs that were reported in the 7 days following the subject's completion/discontinuation visit.

Adverse event reporting additional description:

Only treatment emergent AEs were summarised. A treatment emergent AE was defined as any AE with an onset date on or after the first dose of IMP if the AE was absent before the first dose of IMP, or worsened after the first dose of IMP.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Flutiform High Dose
Reporting group description:	
Flutiform 250/10 µg (2 puffs BID)	
Reporting group title	Flutiform Medium Dose
Reporting group description:	
Flutiform 125/5 µg (2 puffs BID)	
Reporting group title	Formoterol
Reporting group description:	
Formoterol 12 µg (1 puff BID)	

Serious adverse events	Flutiform High Dose	Flutiform Medium Dose	Formoterol
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 587 (10.73%)	75 / 588 (12.76%)	58 / 590 (9.83%)
number of deaths (all causes)	21	21	13
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	3 / 590 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			

subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
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 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 587 (0.00%)	2 / 588 (0.34%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	2 / 587 (0.34%)	1 / 588 (0.17%)	2 / 590 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Prostatic adenoma			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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 cancer metastatic			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord neoplasm			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Vocal cord neoplasm			

subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Circulatory collapse			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Deep vein thrombosis			
subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Embolism arterial			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Haematoma			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Hypertension			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	2 / 590 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant hypertension			

subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	0 / 590 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Varicose vein			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 587 (0.51%)	3 / 588 (0.51%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 3	0 / 1
Sudden death			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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			
Acute respiratory failure			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Asphyxia			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Haemoptysis			
subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	2 / 590 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	0 / 590 (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
Pulmonary embolism			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Pulmonary hypertension			
subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary mass			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 587 (0.00%)	3 / 588 (0.51%)	3 / 590 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Vocal cord leukoplakia			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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			
Affective disorder			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Completed suicide			
subjects affected / exposed	2 / 587 (0.34%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Suicide attempt			

subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Alcohol poisoning			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Femur fracture			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Hip fracture			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Lower limb fracture			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Tibia fracture			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Pain in extremity			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
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			
Acute coronary syndrome			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute left ventricular failure			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Angina pectoris			

subjects affected / exposed	1 / 587 (0.17%)	2 / 588 (0.34%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	3 / 590 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	3 / 587 (0.51%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	5 / 587 (0.85%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure chronic			

subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Congestive cardiomyopathy			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	4 / 587 (0.68%)	3 / 588 (0.51%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Myocardial infarction			
subjects affected / exposed	1 / 587 (0.17%)	2 / 588 (0.34%)	3 / 590 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			

subjects affected / exposed	0 / 587 (0.00%)	2 / 588 (0.34%)	2 / 590 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pericarditis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary valve incompetence			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Right ventricular failure			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Sick sinus syndrome			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Ventricular arrhythmia			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Ventricular extrasystoles			

subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 587 (0.00%)	3 / 588 (0.51%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 587 (0.34%)	0 / 588 (0.00%)	3 / 590 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 587 (0.00%)	2 / 588 (0.34%)	0 / 590 (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
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
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 / 587 (0.00%)	1 / 588 (0.17%)	2 / 590 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Inguinal hernia			
subjects affected / exposed	2 / 587 (0.34%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			

subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Large intestine perforation			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Large intestine polyp			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Mesenteric artery thrombosis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Oesophagitis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Papilla of Vater stenosis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Umbilical hernia			

subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Cholecystitis			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Cholecystitis acute			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Swelling face			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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 and urinary disorders			
Diabetic nephropathy			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Haematuria			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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

Nephrotic syndrome			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
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 failure			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Renal failure acute			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Spondyloarthropathy			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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			
Appendicitis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Bronchiolitis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Bronchitis			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Bronchitis haemophilus			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Bronchopneumonia			
subjects affected / exposed	0 / 587 (0.00%)	2 / 588 (0.34%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Infection			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Influenza			

subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (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
Laryngitis			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 587 (0.17%)	1 / 588 (0.17%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 587 (0.17%)	0 / 588 (0.00%)	0 / 590 (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
Orchitis			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	14 / 587 (2.39%)	16 / 588 (2.72%)	7 / 590 (1.19%)
occurrences causally related to treatment / all	0 / 14	2 / 17	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
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 / 587 (0.00%)	0 / 588 (0.00%)	2 / 590 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 587 (0.00%)	0 / 588 (0.00%)	1 / 590 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 587 (0.00%)	1 / 588 (0.17%)	0 / 590 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Flutiform High Dose	Flutiform Medium Dose	Formoterol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 587 (10.39%)	61 / 588 (10.37%)	50 / 590 (8.47%)
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 587 (3.24%)	16 / 588 (2.72%)	13 / 590 (2.20%)
occurrences (all)	24	16	14
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	31 / 587 (5.28%)	30 / 588 (5.10%)	30 / 590 (5.08%)
occurrences (all)	38	35	37
Pneumonia			
subjects affected / exposed	17 / 587 (2.90%)	21 / 588 (3.57%)	11 / 590 (1.86%)
occurrences (all)	17	22	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2013	A change to the inclusion criteria was made in order to include subjects with an FEV1 predicted normal measured at screening of ≥ 30% to ≤ 50 %, and to provide specific withdrawal criteria related to worsening of subject's condition. This amendment was applicable to the Czech Republic only.
09 April 2014	This amendment provided a change to the spirometry withhold time for slow release β2-agonists and clarification to the Early Discontinuation / Withdrawal / Loss to Follow-up section of the protocol in order to address Ministry of Food and Drug Safety requests. This amendment was applicable to Republic of Korea only.
09 May 2014	Protocol amendment 3 provided a change to the permitted concomitant therapies to remove regular treatment with SAMA to address a Ministry of Food and Drug Safety request, as SAMA is not used as routine therapy for COPD in Republic of Korea. This amendment was applicable to Republic of Korea only.
19 November 2014	Protocol Amendment 4 provided confirmation of the total number of subjects to be randomised, following blinded review of the primary endpoint data. This was completed as an ongoing review with more than 50% of subjects randomised. The number of subjects was increased by approximately 228 randomised subjects which was within the range of a maximum of 870 additional subjects predicted in the protocol. Other administrative changes were made to document protocol clarifications and correct minor inconsistencies in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported