

**Clinical trial results:****A Phase IIIB, 6-Month, Double-blind, Double-dummy, Randomized, Parallel-group, Multicenter Exacerbation Study of Symbicort® pMDI 160/4.5 g x 2 Actuations Twice-daily Compared to Formoterol Turbuhaler 4.5 g x 2 Inhalations Twice-daily in COPD Patients The RISE study – Revealing the Impact of Symbicort in reducing Exacerbations in COPD****Summary**

EudraCT number	2014-000593-19
Trial protocol	DE CZ ES BG
Global end of trial date	10 February 2016

Results information

Result version number	v1 (current)
This version publication date	24 February 2017
First version publication date	24 February 2017

Trial information**Trial identification**

Sponsor protocol code	D589UC00001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden,
Public contact	Tor Skärby, AstraZeneca, +46 x, tor.skarby@astrazeneca.com
Scientific contact	Tor Skärby, AstraZeneca, +46 x, tor.skarby@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2016
Global end of trial reached?	Yes
Global end of trial date	10 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy in reducing exacerbations with Symbicort pMDI 160/4.5 µg x 2 actuations BID versus formoterol Turbuhaler 4.5 µg x 2 inhalations BID in COPD subjects

Protection of trial subjects:

Albuterol or salbutamol was provided as rescue medication at every study visit as needed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2014
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	United States: 500
Country: Number of subjects enrolled	Bulgaria: 159
Country: Number of subjects enrolled	Poland: 159
Country: Number of subjects enrolled	Argentina: 87
Country: Number of subjects enrolled	Germany: 84
Country: Number of subjects enrolled	Czech Republic: 77
Country: Number of subjects enrolled	South Africa: 57
Country: Number of subjects enrolled	Chile: 47
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	Spain: 12
Worldwide total number of subjects	1219
EEA total number of subjects	491

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	674
From 65 to 84 years	535
85 years and over	10

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After the enrollment visit the entry criteria were confirmed and the subject entered a 4- week run-in period with Symbicort pMDI. Patients who still met the eligibility criteria were thereafter randomized to a 26-week treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Symbicort pMDI

Arm description:

Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations BID, for oral inhalation

Arm type	Experimental
Investigational medicinal product name	Symbicort pMDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, powder
Routes of administration	Inhalation use

Dosage and administration details:

160/4.5 ug x2 bid

Arm title	Formoterol Turbuhaler
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Arm description:

Formoterol Turbuhaler, 4.5 µg x 2 actuations BID, for oral inhalation

Arm type	Active comparator
Investigational medicinal product name	Formoterol Turbuhaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

4.5 µg

Number of subjects in period 1	Symbicort pMDI	Formoterol Turbuhaler
Started	606	613
Completed	606	613

Period 2

Period 2 title	Overall Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Symbicort pMDI
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Arm description:

Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations BID, for oral inhalation

Arm type	Experimental
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Investigational medicinal product name	Symbicort pMDI
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Inhalation vapour, powder
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Routes of administration	Inhalation use
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Dosage and administration details:

160/4.5 ug x2 bid

Arm title	Formoterol Turbuhaler
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Arm description:

Formoterol Turbuhaler, 4.5 µg x 2 actuations BID, for oral inhalation

Arm type	Active comparator
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Investigational medicinal product name	Formoterol Turbuhaler
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Inhalation powder
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Routes of administration	Inhalation use
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Dosage and administration details:

4.5 µg

Number of subjects in period 2	Symbicort pMDI	Formoterol Turbuhaler
Started	606	613
Completed	567	548
Not completed	39	65
Adverse event, serious fatal	4	4
Consent withdrawn by subject	25	39
Adverse event, non-fatal	3	5
Other	5	12
Screen failure	1	2
Progressive disease	-	2
Protocol deviation	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Symbicort pMDI
Reporting group description: Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations BID, for oral inhalation	
Reporting group title	Formoterol Turbuhaler
Reporting group description: Formoterol Turbuhaler, 4.5 µg x 2 actuations BID, for oral inhalation	

Reporting group values	Symbicort pMDI	Formoterol Turbuhaler	Total
Number of subjects	606	613	1219
Age categorical Units: Subjects			
Adults (18-64 years)	345	329	674
From 65-84 years	256	279	535
85 years and over	5	5	10
Age Continuous Units: years			
arithmetic mean	63.1	63.9	
standard deviation	± 8.65	± 8.67	-
Gender, Male/Female Units: Participants			
Female	251	270	521
Male	355	343	698
FEV1 post-bronchodilator			
FEV1 post-bronchodilator categories Units: Subjects			
<30%	59	54	113
>=30% to <50%	234	247	481
>=50% to <=70%	307	308	615
>70%	4	3	7
missing value	2	1	3
Number of prior exacerbations			
Number of exacerbations during 2 - 52 weeks prior to enrollment Units: Subjects			
1 exacerbation	430	448	878
2 exacerbations	136	117	253
3 exacerbations	29	28	57
4 exacerbations	7	13	20
5 exacerbations	2	6	8
6 exacerbations	0	1	1
7 exacerbations	2	0	2

End points

End points reporting groups

Reporting group title	Symbicort pMDI
Reporting group description:	Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations BID, for oral inhalation
Reporting group title	Formoterol Turbuhaler
Reporting group description:	Formoterol Turbuhaler, 4.5 µg x 2 actuations BID, for oral inhalation
Reporting group title	Symbicort pMDI
Reporting group description:	Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations BID, for oral inhalation
Reporting group title	Formoterol Turbuhaler
Reporting group description:	Formoterol Turbuhaler, 4.5 µg x 2 actuations BID, for oral inhalation

Primary: The rate of moderate and severe COPD exacerbations defined as: Worsening of ≥2 major symptoms or worsening of 1 major symptom together with ≥1 minor symptom for ≥2 consecutive days

End point title	The rate of moderate and severe COPD exacerbations defined as: Worsening of ≥2 major symptoms or worsening of 1 major symptom together with ≥1 minor symptom for ≥2 consecutive days
End point description:	Moderate exacerbation: treatment of symptoms with systemic corticosteroids (≥3 days) and/or antibiotics. Severe exacerbation: symptoms that require hospitalization (including >24 hours in ED/urgent care setting). Major symptom: -Increased dyspnea -Increase in sputum volume -Increase in sputum color/purulence Minor symptoms: -Sore throat -Colds (nasal discharge and/or nasal congestion) -Fever without other cause -Increased cough -Increased wheeze
End point type	Primary
End point timeframe:	Randomization W 0 to End of Treatment (EoT) W 26

End point values	Symbicort pMDI	Formoterol Turbuhaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	606	613		
Units: annual rate				
least squares mean (confidence interval 95%)	0.85 (0.7 to 1.03)	1.12 (0.93 to 1.35)		

Statistical analyses

Statistical analysis title	Comparison the COPD exacerbation rate
Comparison groups	Symbicort pMDI v Formoterol Turbuhaler

Number of subjects included in analysis	1219
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0059
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.92

Secondary: Time to first moderate or severe COPD exacerbation - event count

End point title	Time to first moderate or severe COPD exacerbation - event count
End point description: Time to first COPD exacerbation in the different treatment arms	
End point type	Secondary
End point timeframe: From randomization to EoT W 26	

End point values	Symbicort pMDI	Formoterol Turbuhaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	606	613		
Units: Patients	171	204		

Statistical analyses

Statistical analysis title	Comparison of time to first COPD exacerbation
Comparison groups	Symbicort pMDI v Formoterol Turbuhaler
Number of subjects included in analysis	1219
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0164
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.96

Secondary: St. George's Respiratory Questionnaire (SGRQ)

End point title	St. George's Respiratory Questionnaire (SGRQ)
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End point description:

St. George's Respiratory Questionnaire for measurement of quality of life in patients with diseases of airways obstruction. Change from baseline over the entire randomized treatment period was summarized and analyzed.

End point type	Secondary
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End point timeframe:

From Run-in W -4 to EoT W 26

End point values	Symbicort pMDI	Formoterol Turbuhaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	589	593		
Units: Total score				
arithmetic mean (standard deviation)	-0.855 (\pm 8.941)	0.442 (\pm 9.457)		

Statistical analyses

Statistical analysis title	Comparison on SGRQ total score
Comparison groups	Symbicort pMDI v Formoterol Turbuhaler
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.343
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.318
upper limit	-0.368

Secondary: Pre-dose/pre-bronchodilator FEV1 at the study site

End point title	Pre-dose/pre-bronchodilator FEV1 at the study site
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End point description:

Measurement of lung function. Change from baseline over the entire randomized treatment period was summarized and analyzed.

End point type	Secondary
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End point timeframe:
From Run-in W -4 to EoT W 26

End point values	Symbicort pMDI	Formoterol Turbuhaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	588	589		
Units: Liter				
arithmetic mean (standard deviation)	0.008 (± 0.21)	-0.025 (± 0.198)		

Statistical analyses

Statistical analysis title	Comparison of FEV1 between two arms
Comparison groups	Symbicort pMDI v Formoterol Turbuhaler
Number of subjects included in analysis	1177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0091
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.053

Secondary: Total rescue medication use (average puffs/day)

End point title	Total rescue medication use (average puffs/day)
End point description:	Use of rescue medication is a measure of symptoms that need to be treated with a short-acting bronchodilator. Change from baseline over the entire randomized treatment period was summarized and analyzed.
End point type	Secondary
End point timeframe:	From Run-in W -4 to EoT W 26

End point values	Symbicort pMDI	Formoterol Turbuhaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	602	607		
Units: puffs/day				
arithmetic mean (standard deviation)	0.135 (\pm 1.248)	0.343 (\pm 1.456)		

Statistical analyses

Statistical analysis title	Comparison of average usage of rescue medication
Comparison groups	Symbicort pMDI v Formoterol Turbuhaler
Number of subjects included in analysis	1209
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0082
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.203
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.353
upper limit	-0.053

Secondary: Nights with awakening due to COPD

End point title	Nights with awakening due to COPD
End point description:	Number of nights awakened due to COPD symptoms correspond to the severity of nocturnal symptoms from COPD. Change from baseline over the entire randomized treatment period was summarized and analyzed.
End point type	Secondary
End point timeframe:	From Run-in W -4 to EoT W 26

End point values	Symbicort pMDI	Formoterol Turbuhaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	603	610		
Units: average awakenings/night				
arithmetic mean (standard deviation)	-0.007 (\pm 0.173)	0.021 (\pm 0.195)		

Statistical analyses

Statistical analysis title	Comparison average night awakening
Comparison groups	Symbicort pMDI v Formoterol Turbuhaler
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0048
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	-0.009

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the randomized treatment period, ie from first treatment to one day after the last treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Symbicort 160/4.5 ug x2 bid
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Reporting group description: -

Reporting group title	Formoterol 4.5 ug x2 bid
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Reporting group description: -

Serious adverse events	Symbicort 160/4.5 ug x2 bid	Formoterol 4.5 ug x2 bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 605 (8.10%)	63 / 613 (10.28%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			

subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device malfunction			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 605 (0.33%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	20 / 605 (3.31%)	28 / 613 (4.57%)	
occurrences causally related to treatment / all	2 / 22	2 / 29	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic respiratory failure			

subjects affected / exposed	2 / 605 (0.33%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 605 (0.33%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Extradural haematoma			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 605 (0.33%)	2 / 613 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 605 (0.17%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cardiac failure		
subjects affected / exposed	0 / 605 (0.00%)	2 / 613 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure acute		
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure congestive		
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardio-respiratory arrest		
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cardiogenic shock		
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Coronary artery disease		
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial infarction		
subjects affected / exposed	2 / 605 (0.33%)	0 / 613 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Myocardial ischaemia		

subjects affected / exposed	1 / 605 (0.17%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinoatrial block			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal lymphadenopathy			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	1 / 605 (0.17%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 605 (0.17%)	2 / 613 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 605 (0.00%)	2 / 613 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 605 (0.00%)	2 / 613 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			

subjects affected / exposed	1 / 605 (0.17%)	2 / 613 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 605 (0.00%)	5 / 613 (0.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella bacteraemia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 605 (0.17%)	0 / 613 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 605 (0.17%)	2 / 613 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 605 (0.00%)	1 / 613 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Symbicort 160/4.5 ug x2 bid	Formoterol 4.5 ug x2 bid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 605 (6.28%)	56 / 613 (9.14%)	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	8 / 605 (1.32%)	27 / 613 (4.40%)	
occurrences (all)	8	31	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	30 / 605 (4.96%)	32 / 613 (5.22%)	
occurrences (all)	34	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported