



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 |
|-----------------------|-------------|

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 | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

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 |
|------------------|-----------------------|

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, Data analyst, Carer, Assessor |

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 |
|------------------|-----------------------|

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 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) |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

End point description:

Measurement of lung function. 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 | 588 | 589 | | |
| Units: Liter | | | | |
| arithmetic mean (standard deviation) | 0.008 (\pm 0.21) | -0.025 (\pm 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 | Comparision 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 |
|-----------------|------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Symbicort 160/4.5 ug x2 bid |
|-----------------------|-----------------------------|

Reporting group description: -

| | |
|-----------------------|--------------------------|
| Reporting group title | Formoterol 4.5 ug x2 bid |
|-----------------------|--------------------------|

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