

**Clinical trial results:**

A 12-Week, Double-Blind, Randomised, Multi-Centre, Parallel-Group Study Evaluating the Efficacy, Safety, and Patient Use (User Study) of Symbicort®1 (Budesonide/Formoterol) Breath-Actuated Metered Dose Inhaler (BA MDI) 2x160/4.5 g Twice Daily Compared with Symbicort® (Budesonide/Formoterol) AC (Actuation Counter) pMDI 2x160/4.5 g Twice Daily and Budesonide AC pMDI 2x160 g Twice Daily in Adult and Adolescent Asthmatics

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-002523-17 |
| Trial protocol | HU BG |
| Global end of trial date | 02 March 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 01 February 2017 |
| First version publication date | 05 August 2015 |

Trial information**Trial identification**

| | |
|-----------------------|-------------|
| Sponsor protocol code | D589OC00003 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AstraZeneca |
| Sponsor organisation address | AstraZeneca R&D, SE-431 83 Mölndal, Sweden, |
| Public contact | Dr Ulf Nihlen, MD, AstraZeneca, aztrial_results_posting@astrazeneca.com |
| Scientific contact | Dr Ulf Nihlen, MD, AstraZeneca, aztrial_results_posting@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 | 02 March 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 March 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 March 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of Symbicort BA MDI 2x160/4.5 µg bid with that of Symbicort AC pMDI 2x160/4.5 µg bid by evaluation of: forced expiratory volume during first second (FEV1), 60 minutes post-dose and FEV1 pre-dose.

Protection of trial subjects:

The Institutional review board (IRB)/independent ethics committee (IEC) for each study site approved the final clinical study protocol (CSP), including the final version of the informed consent form (ICF) and any other written information and/or materials that were provided to the patients.

The PI at each centre ensured that each patient was given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Each patient was notified that they were free to discontinue from the study at any time. Patients were given the opportunity to ask questions and were allowed time to consider the information provided.

The PI at each centre ensured that each patient provided signed and dated informed consent before conducting any procedure specifically for the study. In patients below the age of consent, informed consent was obtained from both the patient and the patient's parent/legal guardian

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 28 November 2011 |
| 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 | Hungary: 38 |
| Country: Number of subjects enrolled | United States: 150 |
| Country: Number of subjects enrolled | Bulgaria: 26 |
| Worldwide total number of subjects | 214 |
| EEA total number of subjects | 64 |

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) | 21 |
| Adults (18-64 years) | 178 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This was a multicentre trial conducted in 3 countries between November 2011 and August 2012.

Pre-assignment

Screening details:

The study consisted from an enrolment visit, a 2- week run in (standardization) period, randomization at visit 4, and 3 further visits (visits 5- 7) at 3, 7 and 12 weeks. During the 2-week-run-in period patients were treated with budesonide AC pMDI 2x160µg bid. After this period subjects were randomized to receive 1 of 3 doouble blinded treatments.

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, Carer, Assessor |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Symbicort BA MDI |

Arm description:

Symbicort BA MDI 2x160/4.5 µg twice daily

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Symbicort BA MDI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Symbicort BA MDI 2x160/4.5 µg twice daily

| | |
|------------------|----------------|
| Arm title | Symbicort pMDI |
|------------------|----------------|

Arm description:

Symbicort AC pDMI 2x160/4.5 µg twice daily

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

Dosage and administration details:

Symbicort pMDI 2x160/4.5 µg twice daily

| | |
|------------------|------------|
| Arm title | Budesonide |
|------------------|------------|

Arm description:

Budesonide AC pMDI 2x160 µg twice daily

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|-------------------|
| Investigational medicinal product name | Budesonide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Budesonide pMDI 2x160 µg twice daily

| Number of subjects in period 1 | Symbicort BA MDI | Symbicort pMDI | Budesonide |
|---------------------------------------|------------------|----------------|------------|
| Started | 71 | 71 | 72 |
| Completed | 63 | 67 | 65 |
| Not completed | 8 | 4 | 7 |
| Consent withdrawn by subject | 4 | - | 2 |
| Adverse event, non-fatal | 2 | 3 | 3 |
| Eligibility criteria + other | 2 | 1 | 1 |
| Protocol deviation | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Symbicort BA MDI |
| Reporting group description: Symbicort BA MDI 2x160/4.5 µg twice daily | |
| Reporting group title | Symbicort pMDI |
| Reporting group description: Symbicort AC pMDI 2x160/4.5 µg twice daily | |
| Reporting group title | Budesonide |
| Reporting group description: Budesonide AC pMDI 2x160 µg twice daily | |

| Reporting group values | Symbicort BA MDI | Symbicort pMDI | Budesonide |
|---|------------------|----------------|------------|
| Number of subjects | 71 | 71 | 72 |
| 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) | 6 | 8 | 7 |
| Adults (18-64 years) | 60 | 56 | 62 |
| From 65-84 years | 5 | 7 | 3 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 42.83 | 42.62 | 42.72 |
| standard deviation | ± 16.156 | ± 16.873 | ± 14.424 |
| Gender, Male/Female Units: Participants | | | |
| Female | 37 | 47 | 35 |
| Male | 34 | 24 | 37 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 4 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 1 |
| Black or African American | 9 | 7 | 11 |
| White | 57 | 63 | 57 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 0 | 2 |
| Years since asthma diagnosis Units: years | | | |
| arithmetic mean | 24.26 | 24.12 | 24.38 |
| standard deviation | ± 14.891 | ± 15.128 | ± 15.183 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 214 | | |
| 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) | 21 | | |
| Adults (18-64 years) | 178 | | |
| From 65-84 years | 15 | | |
| 85 years and over | 0 | | |
| Age Continuous Units: Years arithmetic mean standard deviation | - | | |
| Gender, Male/Female Units: Participants | | | |
| Female | 119 | | |
| Male | 95 | | |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 6 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| Black or African American | 27 | | |
| White | 177 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 3 | | |
| Years since asthma diagnosis Units: years arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Symbicort BA MDI |
| Reporting group description: Symbicort BA MDI 2x160/4.5 µg twice daily | |
| Reporting group title | Symbicort pMDI |
| Reporting group description: Symbicort AC pMDI 2x160/4.5 µg twice daily | |
| Reporting group title | Budesonide |
| Reporting group description: Budesonide AC pMDI 2x160 µg twice daily | |

Primary: Forced expiratory volume in 1 second (FEV1) - Post dose

| | |
|--|---|
| End point title | Forced expiratory volume in 1 second (FEV1) - Post dose |
| End point description: Descriptive statistics for post-dose FEV1 (L) by visit; Baseline defined as the last pre-dose value prior to 1st dose of randomized therapy. Trt Avg = Mean of all available valid values after randomization. | |
| End point type | Primary |
| End point timeframe: 60 minutes post-dose in clinic visits at baseline, and week 3, 7, 12 | |

| End point values | Symbicort BA MDI | Symbicort pMDI | Budesonide | |
|---|------------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 71 | 71 | |
| Units: Liter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Baseline (Week 0) | 2.09 (± 31.46) | 1.97 (± 27.16) | 2.12 (± 26.34) | |
| Week 0 | 2.49 (± 32.14) | 2.35 (± 25.97) | 2.28 (± 27.18) | |
| Week 3 | 2.52 (± 31.98) | 2.34 (± 26.31) | 2.3 (± 30.22) | |
| Week 7 | 2.59 (± 32.17) | 2.35 (± 27.22) | 2.33 (± 29.29) | |
| Week 12 | 2.52 (± 30.71) | 2.39 (± 27.31) | 2.3 (± 28.27) | |
| Treatment Average | 2.53 (± 30.57) | 2.37 (± 26.33) | 2.3 (± 28.36) | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | FEV1 - Symbicort pMDI vs Budesonide |
| Statistical analysis description: The comparison of Symbicort AC pMDI 2x160/4.5 µg bid with budesonide AC pMDI 2x160 µg bid for post dose FEV1 | |
| Comparison groups | Symbicort pMDI v Budesonide |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Estimated Geometric Mean Ratio |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.14 |

| | |
|-----------------------------------|---|
| Statistical analysis title | FEV1 - Symbicort BA MDI vs Symbicort pMDI |
|-----------------------------------|---|

Statistical analysis description:

The comparisons of Symbicort BA MDI 2x160/4.5 µg bid with Symbicort AC pMDI 2x160/4.5 µg bid for post dose FEV1.

| | |
|---|-----------------------------------|
| Comparison groups | Symbicort BA MDI v Symbicort pMDI |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.547 |
| Method | ANCOVA |
| Parameter estimate | Estimated Geometric Mean Ratio |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.05 |

Notes:

[1] - Assuming a standard deviation of 0.2 (for pre dose FEV1) on the log-scale and 60 patients/arm, the width of the confidence interval will extend 0.072 from the point estimate on the log-scale. The lower and upper limits of the CI for the ratio of effects will thus be obtained by multiplying the estimated ratio by 0.931 and 1.075, respectively.

Primary: Forced expiratory volume in 1 second (FEV1) - Pre dose

| | |
|-----------------|--|
| End point title | Forced expiratory volume in 1 second (FEV1) - Pre dose |
|-----------------|--|

End point description:

Descriptive statistics for predose FEV1(L) by visit; Baseline defined as the last pre-dose value prior to 1st dose of randomized therapy. Trt Avg = Mean of all available valid values after randomization.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre AM dose in clinic visits at baseline, and week 3, 7, 12

| End point values | Symbicort BA MDI | Symbicort pMDI | Budesonide | |
|---|------------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 71 | 71 | |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Baseline (Week 0) | 2.09 (± 31.46) | 1.97 (± 27.16) | 2.12 (± 26.34) | |
| Week 3 | 2.32 (± 32.79) | 2.12 (± 28.29) | 2.22 (± 31.21) | |
| Week 7 | 2.4 (± 32.86) | 2.11 (± 29.96) | 2.25 (± 29.01) | |
| Week 12 | 2.34 (± 30.84) | 2.17 (± 31.29) | 2.23 (± 30.15) | |
| Average of treatment period | 2.34 (± 30.15) | 2.15 (± 29.15) | 2.23 (± 29.36) | |

Statistical analyses

| Statistical analysis title | FEV1 pre-dose - Symbicort BA MDI vs Symbicort pMDI |
|---|--|
| Statistical analysis description: The comparisons of Symbicort BA MDI 2x160/4.5 µg bid with Symbicort AC pMDI 2x160/4.5 µg bid, for pre-dose FEV1. | |
| Comparison groups | Symbicort BA MDI v Symbicort pMDI |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.131 |
| Method | ANCOVA |
| Parameter estimate | Estimated Geometric Mean Ratio |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 1.08 |

Notes:

[2] - Assuming a standard deviation of 0.2 (for pre dose FEV1) on the log-scale and 60 patients/arm, the width of the confidence interval will extend 0.072 from the point estimate on the log-scale. The lower and upper limits of the CI for the ratio of effects will thus be obtained by multiplying the estimated ratio by 0.931 and 1.075, respectively.

Secondary: Peak expiratory flow

| | |
|--|----------------------|
| End point title | Peak expiratory flow |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Recorded morning upon rising and evening before sleep for 14 weeks | |

| End point values | Symbicort BA MDI | Symbicort pMDI | Budesonide | |
|--|-------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 71 | 71 | |
| Units: L/Min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Morning Peak expiratory flow (Baseline) | 357.95 (± 100.59) | 335.7 (± 102.99) | 360.46 (± 103.09) | |
| Evening Peak expiratory flow (Baseline) | 364.61 (± 103.62) | 347.86 (± 110.8) | 367.64 (± 102.73) | |
| Evening Peak expiratory flow (Treatment Average) | 379.96 (± 104.72) | 362.99 (± 112.63) | 348.94 (± 97.94) | |
| Morning Peak expiratory flow (Treatment Average) | 376.28 (± 106.76) | 353.69 (± 108.72) | 343.59 (± 98.12) | |

Statistical analyses

| Statistical analysis title | mPEF - Symbicort BA MDI vs Symbicort pMDI |
|--|---|
| Statistical analysis description: | |
| Morning peak expiratory flow (mPEF): Comparing mean changes from baseline to the average of the double-blind treatment period between Symbicort BA MDI 2x160/4.5 µg bid and Symbicort AC pMDI 2x160/4.5 µg bid | |
| Comparison groups | Symbicort BA MDI v Symbicort pMDI |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.825 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.81 |
| upper limit | 14.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.75 |

Notes:

[3] - No adjustment were be made for multiplicity for these supportive variables and nominal p-values were reported.

| Statistical analysis title | mPEF - Symbicort pMDI vs Budesonide |
|--|-------------------------------------|
| Statistical analysis description: | |
| Morning peak expiratory flow (mPEF): Comparing mean changes from baseline to the average of the double-blind treatment period between Symbicort AC pMDI 2x160/4.5 µg bid minus Budesonide AC pMDI 2x160 µg bid | |
| Comparison groups | Symbicort pMDI v Budesonide |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 33.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.11 |
| upper limit | 46.93 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.8 |

| | |
|-----------------------------------|---|
| Statistical analysis title | ePEF - Symbicort BA MDI vs Symbicort pMDI |
|-----------------------------------|---|

Statistical analysis description:

Evening peak expiratory flow (ePEF): Comparing mean changes from baseline to the average of the double-blind treatment period between Symbicort BA MDI 2x160/4.5 µg bid and Symbicort AC pMDI 2x160/4.5 µg bid.

| | |
|---|-----------------------------------|
| Comparison groups | Symbicort BA MDI v Symbicort pMDI |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.81 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.66 |
| upper limit | 13.61 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.15 |

Notes:

[4] - No adjustment were made for multiplicity for these supportive variables and nominal p-values were reported.

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | ePEF - Symbicort pMDi vs Budesonide |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Evening peak expiratory flow (ePEF): Comparing mean changes from baseline to the average of the double-blind treatment period between Symbicort AC pMDI 2x160/4.5 µg bid and Budesonide AC pMDI 2x160 µg bid.

| | |
|-------------------|-----------------------------|
| Comparison groups | Symbicort pMDI v Budesonide |
|-------------------|-----------------------------|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 32.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.01 |
| upper limit | 44.49 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.21 |

Secondary: Asthma symptoms Score (Total)

| | |
|---|-------------------------------|
| End point title | Asthma symptoms Score (Total) |
| End point description: | |
| The total score is calculated as sum of the morning and evening scores of each day and the treatment period mean score is defined as the mean of all total score recorded during the 12-week treatment period. Trt Avg=Mean total score of double-blind period values.(day/night score ranges from 0 to 3; 0=no asthma symptoms; 3= unable to do normal activities (or to sleep) due to asthma). Higher score represents worse outcome. | |
| End point type | Secondary |
| End point timeframe: | |
| Recorded between 6:00 – 11:00 AM from previous 12 hours and 6:00 -11:00 PM from previous 12 hours for 14 weeks | |

| End point values | Symbicort BA MDI | Symbicort pMDI | Budesonide | |
|--|------------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 71 | 71 | |
| Units: Asthma score on a scale of 0 to 3 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 2.04 (± 0.98) | 1.92 (± 0.72) | 2.12 (± 0.88) | |
| Treatment Average (Trt Avg) | 1.68 (± 1.1) | 1.45 (± 0.91) | 2.02 (± 0.96) | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Total Symptom score - Symb. BA MDI vs Symb. pMDI |
| Statistical analysis description: | |
| Comparing mean changes from baseline to the average of the double-blind treatment period between Symbicort BA MDI 2x160/4.5 µg bid and Symbicort AC pMDI 2x160/4.5 µg bid. | |
| Comparison groups | Symbicort BA MDI v Symbicort pMDI |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.272 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.35 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.11 |

Notes:

[5] - No adjustment were made for multiplicity for these supportive variables and nominal p-values were reported.

Secondary: Night-time awakenings due to asthma symptoms(% Awakening-free nights)

| | |
|-----------------|---|
| End point title | Night-time awakenings due to asthma symptoms(% Awakening-free nights) |
|-----------------|---|

End point description:

The percentage of days with no awakenings due to asthma. Baseline= Mean % awakening-free nights during run-in period ; Trt Avg=Mean % awakening-free nights during double-blind period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Recorded 6:00 – 11:00 AM for 14 weeks

| End point values | Symbicort BA MDI | Symbicort pMDI | Budesonide | |
|--|------------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 71 | 71 | |
| Units: Percentage of days with no awakenings | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 78.54 (± 28.97) | 78.76 (± 29.76) | 81.59 (± 25.32) | |
| Treatment Average (Trt Avg) | 83.73 (± 30.9) | 89.93 (± 21.4) | 84.62 (± 26.31) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Nighttime Awakenings - Symb. BA MDI vs Symb. pMDI |
|----------------------------|---|

Statistical analysis description:

Comparing mean changes from baseline to the average of the double-blind treatment period between Symbicort BA MDI 2x160/4.5 µg bid and Symbicort AC pMDI 2x160/4.5 µg bid.

| | |
|-------------------|-----------------------------------|
| Comparison groups | Symbicort BA MDI v Symbicort pMDI |
|-------------------|-----------------------------------|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.025 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -6.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.41 |
| upper limit | -0.79 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.69 |

Notes:

[6] - No adjustment were made for multiplicity for these supportive variables and nominal p-values were reported.

Secondary: Use of rescue medication day and night (Total daily rescue medication use)

| | |
|-----------------|--|
| End point title | Use of rescue medication day and night (Total daily rescue medication use) |
|-----------------|--|

End point description:

Total daily rescue medication use is calculated as the sum of morning and evening use each day and averaged over the 12 weeks treatment periods to calculate the treatment period mean. Baseline= Mean rescue medication used during run-in period ; Trt Avg=Mean rescue medication used during double-blind period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Recorded between 6:00 – 11:00 AM from previous 12 hours and 6:00 -11:00 PM from previous 12 hours for 14 weeks

| End point values | Symbicort BA MDI | Symbicort pMDI | Budesonide | |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 71 | 71 | |
| Units: Inhalations/24 hrs | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 2.55 (± 2.48) | 2.19 (± 1.75) | 2.65 (± 2.36) | |
| Treatment Average (Trt Avg) | 1.81 (± 2.67) | 1.26 (± 1.6) | 2.34 (± 2.38) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Total Daily Rescue Med-Symb. BA MDI vs Symb. pMDI |
|----------------------------|---|

Statistical analysis description:

Comparing mean changes from baseline to the average of the double-blind treatment period between BAI Symbicort BA MDI 2x160/4.5 µg bid and pMDI Symbicort AC pMDI 2x160/4.5 µg bid.

| | |
|-------------------|-----------------------------------|
| Comparison groups | Symbicort BA MDI v Symbicort pMDI |
|-------------------|-----------------------------------|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.258 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.19 |
| upper limit | 0.71 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.23 |

Notes:

[7] - No adjustment were made for multiplicity for these supportive variables and nominal p-values were reported.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the enrolment visit (visit 1) until follow-up (14 weeks after randomisation). Events occurring on or after first dose of study medication are included in the summaries.

Adverse event reporting additional description:

1 patient from the Budesonide group has not taken any dose of the IP, so not included in the Safety population'.

A total of 19 patients reported non-serious adverse events; 19 on Budesonide, 21 on Symbicort BA MDI, 24 on Symbicort pMDI.. Numbers for non-serious AEs in the reporting group table are based on the 2% threshold frequency.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Budesonide |
|-----------------------|------------|

Reporting group description:

Budesonide AC pMDI 2x160 µg twice daily

| | |
|-----------------------|------------------|
| Reporting group title | Symbicort BA MDI |
|-----------------------|------------------|

Reporting group description:

Symbicort BA MDI 2x160/4.5 µg twice daily

| | |
|-----------------------|----------------|
| Reporting group title | Symbicort pMDI |
|-----------------------|----------------|

Reporting group description:

Symbicort AC pMDI 2x160/4.5 µg twice daily

| Serious adverse events | Budesonide | Symbicort BA MDI | Symbicort pMDI |
|---|----------------|------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 71 (1.41%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Infections and infestations | | | |
| APPENDICITIS | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 0 / 71 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 | Budesonide | Symbicort BA MDI | Symbicort pMDI |
|---|----------------|------------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 71 (8.45%) | 6 / 71 (8.45%) | 9 / 71 (12.68%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 1 / 71 (1.41%) | 2 / 71 (2.82%) |
| occurrences (all) | 3 | 1 | 2 |
| Infections and infestations | | | |
| VIRAL UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 2 / 71 (2.82%) | 5 / 71 (7.04%) |
| occurrences (all) | 3 | 2 | 5 |
| UPPER RESPIRATORY TRACT INFECTION BACTERIAL | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 2 / 71 (2.82%) | 0 / 71 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | 3 / 71 (4.23%) |
| occurrences (all) | 0 | 1 | 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 13 October 2011 | Clarify the timing of spirometry measurements in the morning. To allow the patients to undergo rescreen, so that at rescreening the patients would meet the time requirements for various elements by Visit 2 in the inclusion criteria without changing the patient characterisation in the study or jeopardizing patient safety. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|--|
| No. of participants in the safety analysis set is (71 for all the group) as 1 patients from the Budesonide group has not taken any dose of the IP, so not included in the Safety population. |
|--|

Notes: