# Clinical trial results:
# A Randomized, Double Blind, Double Dummy, Placebo Controlled, Parallel Group, 12 Week Clinical Study to Assess the Efficacy and Safety Of 320 or 640 mcg/Day of Beclomethasone Dipropionate Delivered via Breath Actuated Inhaler (BAI) or Metered Dose Inhaler (MDI) in Adolescent and Adult Patients 12 Years of Age and Older with Persistent Asthma

## Summary

| | |
|---|---|
| EudraCT number | 2013-003397-27 |
| Trial protocol | HU PL |
| Global end of trial date | 20 November 2014 |

**Results information**

| | |
|---|---|
| Result version number | v3 (current) |
| This version publication date | 23 February 2017 |
| First version publication date | 06 August 2015 |
| Version creation reason | • Correction of full data set<br>AE timeframe needs to be updated |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | BDB-AS-301 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02031640 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Teva Branded Pharmaceutical Products R&D, Inc. |
| Sponsor organisation address | 41 Moores Road, Frazer, Pennsylvania, United States, 19355 |
| Public contact | Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc.<br>, 1 215-591-3000, ustevatrials@tevapharm.com |
| Scientific contact | Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc.<br>, 1 215-591-3000, ustevatrials@tevapharm.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 | 21 July 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 November 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of beclomethasone dipropionate (320 or 640 mcg/day) administered via BAI and MDI compared with placebo treatment in patients with persistent asthma as assessed by the standardized baseline-adjusted trough morning forced expiratory volume in 1 second (FEV1) area under the effect curve from time 0 to 12 weeks (AUEC(0-12wk)).

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) GCP Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union (EU) Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Information regarding any investigational study centers participating in this study that could not comply with these standards was documented.
Written and/or oral information about the study was provided to all patients (or legal guardian of patients under the age of 18) in a language understandable by the patients and per applicable local regulations. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in a consent form that was signed by the patient/parent/guardian with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 02 January 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: 415 |
| Country: Number of subjects enrolled | Poland: 31 |
| Country: Number of subjects enrolled | Germany: 46 |
| Country: Number of subjects enrolled | Hungary: 40 |

| | |
|---|---|
| Worldwide total number of subjects | 532 |
| EEA total number of subjects | 117 |

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) | 26 |
| Adults (18-64 years) | 457 |
| From 65 to 84 years | 48 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Of the 1113 patients screened, 701 were enrolled. Of the 412 patients who were not enrolled, 342 were excluded on the basis of inclusion/exclusion criteria, 29 patients withdrew consent, 26 patients for other reasons, 14 patients were lost to follow up before the baseline visit, and 1 patient due to an adverse event.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Patients administered 4 inhalations from each of the 2 devices twice daily as per the double dummy study design: 1 treatment device or placebo and 1 placebo device for a total of 8 inhalations each time.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Patients took 4 inhalations of matching placebo breath actuated inhaler (BAI) (twice daily) plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo MDI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations. Placebo was delivered via the metered-dose inhaler (MDI) in order to maintain the blind.

| | |
|---|---|
| Investigational medicinal product name | Placebo BAI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations. Placebo was delivered via the breath-actuated inhaler (BAI) in order to maintain the blind.

| | |
|---|---|
| **Arm title** | BAI 320 mcg/day |

Arm description:

Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | beclomethasone dipropionate BAI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 320 mcg/day.

| | |
|---|---|
| Investigational medicinal product name | Placebo MDI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations. Placebo was delivered via the metered-dose inhaler (MDI) in order to maintain the blind.

| | |
|---|---|
| **Arm title** | BAI 640 mcg/day |

Arm description:

Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | beclomethasone dipropionate BAI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 640 mcg/day.

| | |
|---|---|
| Investigational medicinal product name | Placebo MDI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations. Placebo was delivered via the metered-dose inhaler (MDI) in order to maintain the blind.

| | |
|---|---|
| **Arm title** | MDI 320 mcg/day |

Arm description:

Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via metered-dose inhaler (MDI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo breath-actuated inhaler (BAI) (twice daily) for 12 weeks.

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

| | |
|---|---|
| Investigational medicinal product name | beclomethasone dipropionate MDI |
| Investigational medicinal product code | |
| Other name | QVAR® Inhalation Aerosol |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via metered-dose inhaler (MDI) (twice daily) totaling 320 mcg/day.

| | |
|---|---|
| Investigational medicinal product name | Placebo BAI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations. Placebo was delivered via the breath-actuated inhaler (BAI) in order to maintain the blind.

| | |
|---|---|
| **Arm title** | MDI 640 mcg/day |

Arm description:

Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via metered dose inhaler (MDI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo breath actuated inhaler (BAI) (twice daily) for 12 weeks.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | beclomethasone dipropionate MDI |
| Investigational medicinal product code | |
| Other name | QVAR® Inhalation Aerosol |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via metered-dose inhaler (MDI) (twice daily) totaling 640 mcg/day.

| | |
|---|---|
| Investigational medicinal product name | Placebo BAI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Study drug was administered twice each day, in the morning and in the evening, after the completion of the asthma symptoms score and the peak expiratory flow (PEF) measurements, in that order. Each administration consisted of four inhalations. Placebo was delivered via the breath-actuated inhaler (BAI) in order to maintain the blind.

| **Number of subjects in period 1** | Placebo | BAI 320 mcg/day | BAI 640 mcg/day |
|---|---|---|---|
| Started | 106 | 106 | 106 |
| Completed | 84 | 100 | 99 |
| Not completed | 22 | 6 | 7 |
| Consent withdrawn by subject | 2 | 3 | 1 |
| Adverse event, non-fatal | - | - | 2 |
| Non-compliance | 1 | - | 1 |
| Lost to follow-up | 3 | - | - |
| Protocol deviation | 2 | - | 1 |
| Lack of efficacy | 14 | 3 | 2 |

| **Number of subjects in period 1** | MDI 320 mcg/day | MDI 640 mcg/day |
|---|---|---|
| Started | 107 | 107 |
| Completed | 96 | 104 |
| Not completed | 11 | 3 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | - | - |
| Non-compliance | 1 | - |
| Lost to follow-up | 1 | - |
| Protocol deviation | 3 | 1 |
| Lack of efficacy | 5 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients took 4 inhalations of matching placebo breath actuated inhaler (BAI) (twice daily) plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |
| Reporting group title | BAI 320 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |
| Reporting group title | BAI 640 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |
| Reporting group title | MDI 320 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via metered-dose inhaler (MDI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo breath-actuated inhaler (BAI) (twice daily) for 12 weeks. | |
| Reporting group title | MDI 640 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via metered dose inhaler (MDI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo breath actuated inhaler (BAI) (twice daily) for 12 weeks. | |

| Reporting group values | Placebo | BAI 320 mcg/day | BAI 640 mcg/day |
|---|---|---|---|
| Number of subjects | 106 | 106 | 106 |
| Age categorical<br>Units: Subjects | | | |
| 12-17 years | 4 | 5 | 7 |
| 18-64 years | 94 | 86 | 92 |
| >=65 years | 8 | 15 | 7 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 43.7 | 47.9 | 46.2 |
| standard deviation | ± 15.41 | ± 15.54 | ± 14.78 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 68 | 69 | 67 |
| Male | 38 | 37 | 39 |
| Race<br>Units: Subjects | | | |
| White | 73 | 85 | 87 |
| Black | 27 | 18 | 14 |
| Other | 6 | 3 | 5 |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 97 | 95 | 100 |

| | | | |
|---|---|---|---|
| Hispanic or Latino | 9 | 11 | 6 |
| Duration of Asthma<br>Units: Subjects | | | |
| < 3 months | 0 | 0 | 0 |
| 3 months to < 6 months | 0 | 0 | 0 |
| 6 months to < 1 year | 1 | 1 | 0 |
| 1 year to < 5 years | 2 | 4 | 10 |
| 5 years to < 10 years | 15 | 11 | 19 |
| 10 years to < 15 years | 19 | 10 | 22 |
| >= 15 years | 69 | 80 | 55 |
| Weight<br>Units: kg | | | |
| arithmetic mean | 84.54 | 86.17 | 86.26 |
| standard deviation | ± 25.426 | ± 22.399 | ± 21.675 |
| Height<br>Units: cm | | | |
| arithmetic mean | 167.59 | 169.35 | 168.42 |
| standard deviation | ± 9.112 | ± 9.435 | ± 9.465 |
| Body Mass Index<br>Units: kg/m^2 | | | |
| arithmetic mean | 30.08 | 30.01 | 30.371 |
| standard deviation | ± 8.8862 | ± 7.4355 | ± 7.2111 |

| **Reporting group values** | MDI 320 mcg/day | MDI 640 mcg/day | Total |
|---|---|---|---|
| Number of subjects | 107 | 107 | 532 |
| Age categorical<br>Units: Subjects | | | |
| 12-17 years | 4 | 6 | 26 |
| 18-64 years | 93 | 92 | 457 |
| >=65 years | 10 | 9 | 49 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 46.6 | 46.2 | |
| standard deviation | ± 15.41 | ± 15.03 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 65 | 66 | 335 |
| Male | 42 | 41 | 197 |
| Race<br>Units: Subjects | | | |
| White | 89 | 81 | 415 |
| Black | 16 | 24 | 99 |
| Other | 2 | 2 | 18 |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 100 | 101 | 493 |
| Hispanic or Latino | 7 | 6 | 39 |
| Duration of Asthma<br>Units: Subjects | | | |
| < 3 months | 0 | 0 | 0 |
| 3 months to < 6 months | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| 6 months to < 1 year | 0 | 1 | 3 |
| 1 year to < 5 years | 11 | 7 | 34 |
| 5 years to < 10 years | 12 | 7 | 64 |
| 10 years to < 15 years | 15 | 16 | 82 |
| >= 15 years | 68 | 76 | 348 |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 81.6 | 85.5 | |
| standard deviation | ± 20.277 | ± 19.504 | - |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 167.23 | 169.39 | |
| standard deviation | ± 9.387 | ± 10.858 | - |
| Body Mass Index | | | |
| Units: kg/m^2 | | | |
| arithmetic mean | 29.091 | 29.804 | |
| standard deviation | ± 6.1292 | ± 6.461 | - |

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| Patients took 4 inhalations of matching placebo breath actuated inhaler (BAI) (twice daily) plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |

| Reporting group title | BAI 320 mcg/day |
|---|---|
| Reporting group description: | |
| Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |

| Reporting group title | BAI 640 mcg/day |
|---|---|
| Reporting group description: | |
| Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |

| Reporting group title | MDI 320 mcg/day |
|---|---|
| Reporting group description: | |
| Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via metered-dose inhaler (MDI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo breath-actuated inhaler (BAI) (twice daily) for 12 weeks. | |

| Reporting group title | MDI 640 mcg/day |
|---|---|
| Reporting group description: | |
| Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via metered dose inhaler (MDI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo breath actuated inhaler (BAI) (twice daily) for 12 weeks. | |

### Primary: Standardized baseline adjusted trough morning forced expiratory volume in 1 second (FEV1) area under the effect curve from time 0 to 12 weeks [FEV1 AUEC(0-12wk)]

| End point title | Standardized baseline adjusted trough morning forced expiratory volume in 1 second (FEV1) area under the effect curve from time 0 to 12 weeks [FEV1 AUEC(0-12wk)] |
|---|---|
| End point description: | |
| The baseline pulmonary function measurement was defined as the measurement obtained at randomization visit (Day 1). Pulmonary function measurements (including FEV1) were obtained electronically by spirometry. All pulmonary function test data were submitted to a central reading center for evaluation. The highest FEV1 value from 3 acceptable and 2 repeatable maneuvers (maximum of 5 attempts) was used. | |

| End point type | Primary |
|---|---|
| End point timeframe: | |
| Day 1 (baseline), Weeks 2, 4, 8, 12 | |

| End point values | Placebo | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 105[1] | 104[2] | 106[3] | 106[4] |
| Units: liters | | | | |
| least squares mean (standard error) | 0.056 (± 0.0219) | 0.09 (± 0.0221) | 0.101 (± 0.0221) | 0.041 (± 0.0217) |

Notes:

[1] - Full analysis set- randomized patients with atleast 1 dose of drug and 1 postbaseline trough am FEV1

[2] - Full analysis set- randomized patients with atleast 1 dose of drug and 1 postbaseline trough am FEV1

[3] - Full analysis set- randomized patients with atleast 1 dose of drug and 1 postbaseline trough am FEV1

[4] - Full analysis set- randomized patients with atleast 1 dose of drug and 1 postbaseline trough am FEV1

| End point values | MDI 640 mcg/day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 107[5] | | | |
| Units: liters | | | | |
| least squares mean (standard error) | 0.096 (± 0.0216) | | | |

Notes:

[5] - Full analysis set- randomized patients with atleast 1 dose of drug and 1 postbaseline trough am FEV1

## Statistical analyses

| Statistical analysis title | Primary Analysis: Placebo to BAI 320 mcg/day |
|---|---|

Statistical analysis description:

The primary variable was analyzed using an ANCOVA model with effects due to baseline trough morning FEV1, sex, age, and treatment.

| | |
|---|---|
| Comparison groups | Placebo v BAI 320 mcg/day |
| Number of subjects included in analysis | 209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[6] |
| P-value | = 0.272 [7] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.034 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.027 |
| upper limit | 0.095 |

Notes:

[6] - The study was to be considered positive if the result from the comparison of the highest beclomethasone dipropionate dose (640 mcg/day via BAI) with placebo using the ANCOVA was positive, regardless of the results from the comparisons of all the other beclomethasone dipropionate dose-by-device levels with placebo.

[7] - Statistical significance is <=0.05.

| Statistical analysis title | Primary Analysis: Placebo to BAI 640 m... |
|---|---|

Statistical analysis description:

The primary variable was analyzed using an ANCOVA model with effects due to baseline trough morning

FEV1, sex, age, and treatment.

| | |
|---|---|
| Comparison groups | Placebo v BAI 640 mcg/day |
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[8] |
| P-value | = 0.1415 [9] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.045 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.015 |
| upper limit | 0.106 |

Notes:

[8] - The study was to be considered positive if the result from the comparison of the highest beclomethasone dipropionate dose (640 mcg/day via BAI) with placebo using the ANCOVA was positive, regardless of the results from the comparisons of all the other beclomethasone dipropionate dose-by-device levels with placebo.
[9] - Statistical significance is <=0.05.

| **Statistical analysis title** | Primary Analysis: Placebo to MDI 320 m... |
|---|---|

Statistical analysis description:

The primary variable was analyzed using an ANCOVA model with effects due to baseline trough morning FEV1, sex, age, and treatment.

| | |
|---|---|
| Comparison groups | Placebo v MDI 320 mcg/day |
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | = 0.6356 [11] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.015 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.075 |
| upper limit | 0.046 |

Notes:

[10] - The study was to be considered positive if the result from the comparison of the highest beclomethasone dipropionate dose (640 mcg/day via BAI) with placebo using the ANCOVA was positive, regardless of the results from the comparisons of all the other beclomethasone dipropionate dose-by-device levels with placebo.
[11] - Statistical significance is <=0.05.

| **Statistical analysis title** | Primary Analysis: Placebo to MDI 640 m... |
|---|---|

Statistical analysis description:

The primary variable was analyzed using an ANCOVA model with effects due to baseline trough morning FEV1, sex, age, and treatment.

| | |
|---|---|
| Comparison groups | Placebo v MDI 640 mcg/day |

| | |
|---|---|
| Number of subjects included in analysis | 212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.1932 [13] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.1 |

Notes:

[12] - The study was to be considered positive if the result from the comparison of the highest beclomethasone dipropionate dose (640 mcg/day via BAI) with placebo using the ANCOVA was positive, regardless of the results from the comparisons of all the other beclomethasone dipropionate dose-by-device levels with placebo.

[13] - Statistical significance is <=0.05.

## Secondary: Change from Baseline in Weekly Average of Daily Trough Morning Peak Expiratory Flow (PEF) Over the 12-Week Treatment Period

| | |
|---|---|
| End point title | Change from Baseline in Weekly Average of Daily Trough Morning Peak Expiratory Flow (PEF) Over the 12-Week Treatment Period |

End point description:

A hand-held peak flow meter was provided to patients at the screening visit and used to determine the morning and evening PEF throughout the
course of the study.Daily trough morning PEF assessments were taken pre-dose and pre-rescue bronchodilator over the 12-week treatment period. The patient recorded the highest value of 3 measurements obtained in the morning and evening in the patient diary.
Baseline in trough morning PEF is defined as the average of recorded trough morning PEF assessments over the 7-day window before randomization, including the morning assessment on Day 1 before randomization.

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

End point timeframe:

Days -6 to Day 1 (baseline), Day 2 to Week 12

| End point values | Placebo | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106[14] | 104[15] | 106[16] | 106[17] |
| Units: L/min | | | | |
| least squares mean (standard error) | -5.524 (± 2.5944) | 5.092 (± 2.5625) | 2.895 (± 2.559) | 0.48 (± 2.558) |

Notes:

[14] - Full analysis set

[15] - Full analysis set

[16] - Full analysis set

[17] - Full analysis set

| End point values | MDI 640 mcg/day | | | |
|---|---|---|---|---|

| Subject group type | Reporting group | | | |
|---|---|---|---|---|
| Number of subjects analysed | 107[18] | | | |
| Units: L/min | | | | |
| least squares mean (standard error) | 6.988 (± 2.5298) | | | |

Notes:

[18] - Full analysis set

## Statistical analyses

| **Statistical analysis title** | Change in AM PEF: Placebo to BAI 320 mcg/day |
|---|---|

Statistical analysis description:

The analysis of change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period was performed using a repeated measures mixed model with effects due to baseline weekly average of daily trough morning PEF, sex, age, treatment, time, and time-by-treatment interaction.

| Comparison groups | Placebo v BAI 320 mcg/day |
|---|---|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0036 [19] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 10.616 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.489 |
| upper limit | 17.744 |

Notes:

[19] - Statistical significance is <=0.05.

| **Statistical analysis title** | Change in AM PEF: Placebo to BAI 640 m... |
|---|---|

Statistical analysis description:

The analysis of change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period was performed using a repeated measures mixed model with effects due to baseline weekly average of daily trough morning PEF, sex, age, treatment, time, and time-by-treatment interaction.

| Comparison groups | Placebo v BAI 640 mcg/day |
|---|---|
| Number of subjects included in analysis | 212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0204 [20] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.419 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.309 |
| upper limit | 15.53 |

Notes:

[20] - Statistical significance is <=0.05.

| **Statistical analysis title** | Change in AM PEF: Placebo to MDI 320 m... |
|---|---|

Statistical analysis description:

The analysis of change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period was performed using a repeated measures mixed model with effects due to baseline weekly average of daily trough morning PEF, sex, age, treatment, time, and time-by-treatment interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 320 mcg/day |
| Number of subjects included in analysis | 212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0984 [21] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 6.004 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.121 |
| upper limit | 13.129 |

Notes:

[21] - Statistical significance is <=0.05.

| **Statistical analysis title** | Change in AM PEF: Placebo to MDI 640 m... |
|---|---|

Statistical analysis description:

The analysis of change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period was performed using a repeated measures mixed model with effects due to baseline weekly average of daily trough morning PEF, sex, age, treatment, time, and time-by-treatment interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 640 mcg/day |
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 [22] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 12.512 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.435 |
| upper limit | 19.589 |

Notes:

[22] - Statistical significance is <=0.05.

## Secondary: Change from Baseline in Weekly Average of Daily Evening Peak Expiratory Flow (PEF) Over the 12-Week Treatment Period

| | |
|---|---|
| End point title | Change from Baseline in Weekly Average of Daily Evening Peak Expiratory Flow (PEF) Over the 12-Week Treatment Period |

End point description:

A hand-held peak flow meter was provided to patients at the screening visit and used to determine the morning and evening PEF throughout the course of the study. The patient recorded the highest value of 3 measurements obtained in the morning and evening in the patient diary.
Baseline in evening PEF is defined as the average of recorded evening PEF assessments over the 7-day window before randomization.

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

End point timeframe:

Days -6 to Day 0 (baseline), Day 1 to Week 12

| **End point values** | Placebo | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106[23] | 104[24] | 106[25] | 106[26] |
| Units: L/min | | | | |
| least squares mean (standard error) | -4.708 (± 2.6503) | 4.439 (± 2.6199) | 4.462 (± 2.6092) | -0.62 (± 2.6145) |

Notes:

[23] - Full analysis set

[24] - Full analysis set

[25] - Full analysis set

[26] - Full analysis set

| **End point values** | MDI 640 mcg/day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 107[27] | | | |
| Units: L/min | | | | |
| least squares mean (standard error) | 5.594 (± 2.5848) | | | |

Notes:

[27] - Full analysis set

## Statistical analyses

| **Statistical analysis title** | Change in PM PEF: Placebo to BAI 320 mcg/day |
|---|---|

Statistical analysis description:

The analysis of change from baseline in the weekly average of daily evening PEF over the 12-week treatment period will be performed using a repeated measures mixed model with effects due to baseline weekly average of daily evening PEF, sex, age, treatment, time, and time-by-treatment interaction.

| Comparison groups | Placebo v BAI 320 mcg/day |
|---|---|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0139 [28] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 9.147 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.866 |
| upper limit | 16.429 |

Notes:

[28] - Statistical significance is <=0.05.

| **Statistical analysis title** | Change in PM PEF: Placebo to BAI 640 mc... |
|---|---|

Statistical analysis description:

The analysis of change from baseline in the weekly average of daily evening PEF over the 12-week treatment period will be performed using a repeated measures mixed model with effects due to baseline weekly average of daily evening PEF, sex, age, treatment, time, and time-by-treatment interaction.

| | |
|---|---|
| Comparison groups | Placebo v BAI 640 mcg/day |
| Number of subjects included in analysis | 212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0133 [29] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 9.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.914 |
| upper limit | 16.425 |

Notes:

[29] - Statistical significance is <=0.05.

| **Statistical analysis title** | Change in PM PEF: Placebo to MDI 320 mc... |
|---|---|

Statistical analysis description:

The analysis of change from baseline in the weekly average of daily evening PEF over the 12-week treatment period will be performed using a repeated measures mixed model with effects due to baseline weekly average of daily evening PEF, sex, age, treatment, time, and time-by-treatment interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 320 mcg/day |
| Number of subjects included in analysis | 212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2704 [30] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.088 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.191 |
| upper limit | 11.367 |

Notes:

[30] - Statistical significance is <=0.05.

| **Statistical analysis title** | Change in PM PEF: Placebo to MDI 640 mc... |
|---|---|

Statistical analysis description:

The analysis of change from baseline in the weekly average of daily evening PEF over the 12-week treatment period will be performed using a repeated measures mixed model with effects due to baseline weekly average of daily evening PEF, sex, age, treatment, time, and time-by-treatment interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 640 mcg/day |
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0053 [31] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 10.301 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.073 |
| upper limit | 17.53 |

Notes:

[31] - Statistical significance is <=0.05.

## Secondary: Change from Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol Over Weeks 1-12

| | |
|---|---|
| End point title | Change from Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol Over Weeks 1-12 |

End point description:

Change from baseline in the use of rescue medication, albuterol/salbutamol, during the treatment period offers an indication of asthma control. Baseline was defined as the average of recorded daily usage of albuterol/salbutamol inhalation aerosol over the 7 days prior to the first dose of double-blind study treatment, including the morning usage at the randomization visit.

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

End point timeframe:

Days -6 to Day 1 (baseline), Day 2 to Week 12

| End point values | Placebo | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 101[32] | 96[33] | 99[34] | 97[35] |
| Units: number of inhalations | | | | |
| least squares mean (standard error) | 0.478 (± 0.1232) | -0.226 (± 0.1235) | -0.213 (± 0.1221) | -0.173 (± 0.1246) |

Notes:

[32] - Full analysis set

[33] - Full analysis set

[34] - Full analysis set

[35] - Full analysis set

| End point values | MDI 640 mcg/day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 101[36] | | | |
| Units: number of inhalations | | | | |

| | | | | |
|---|---|---|---|---|
| least squares mean (standard error) | -0.323 (± 0.1206) | | | |

Notes:

[36] - Full analysis set

## Statistical analyses

| **Statistical analysis title** | Use of Rescue Med: Placebo to BAI 320 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| | |
|---|---|
| Comparison groups | Placebo v BAI 320 mcg/day |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [37] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.703 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.044 |
| upper limit | -0.363 |

Notes:

[37] - Statistical significance is <=0.05.

| **Statistical analysis title** | Use of Rescue Med: Placebo to BAI 640 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| | |
|---|---|
| Comparison groups | Placebo v BAI 640 mcg/day |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [38] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.691 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.029 |
| upper limit | -0.352 |

Notes:

[38] - Statistical significance is <=0.05.

| **Statistical analysis title** | Use of Rescue Med: Placebo to MDI 320 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 320 mcg/day |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 [39] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.651 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.994 |
| upper limit | -0.309 |

Notes:

[39] - Statistical significance is <=0.05.

| **Statistical analysis title** | Use of Rescue Med: Placebo to MDI 640 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 640 mcg/day |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [40] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.801 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.138 |
| upper limit | -0.464 |

Notes:

[40] - Statistical significance is <=0.05.

## Secondary: Change from Baseline in Weekly Average of Total Daily Asthma Symptom Score over Weeks 1-12

| End point title | Change from Baseline in Weekly Average of Total Daily Asthma Symptom Score over Weeks 1-12 |
|---|---|

End point description:

The daily asthma score is the average of the daytime and nighttime scores over weeks 1-12. Asthma symptom scores are recorded in the patient's diary each morning and each evening before determining PEF and before administration of study or rescue medications. The Daytime Symptom Score (determined in the evening) has a range from 0=No symptoms during the day to 5=Symptoms so severe that I could not go to work or perform normal daily activities. The Nighttime Symptom Score (determined in the morning) has a range from 0=No symptoms during the night to 4=Symptoms so severe that I did not sleep at all. The scale for the daily asthma score is therefore 0 (no symptoms) to 9 (severe symptoms).

Baseline was defined as the average of recorded daily asthma symptom scores over the 7 days prior to the first dose of double-blind study treatment, including the morning score at the randomization visit.

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

End point timeframe:

Days -6 to Day 1 (baseline), Week 1 to Week 12

| **End point values** | Placebo | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106[41] | 104[42] | 106[43] | 106[44] |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -0.058 (± 0.0425) | -0.207 (± 0.0417) | -0.159 (± 0.0415) | -0.247 (± 0.0417) |

Notes:

[41] - Full analysis set

[42] - Full analysis set

[43] - Full analysis set

[44] - Full analysis set

| **End point values** | MDI 640 mcg/day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 107[45] | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -0.274 (± 0.0411) | | | |

Notes:

[45] - Full analysis set

## Statistical analyses

| **Statistical analysis title** | Asthma Symptoms: Placebo to BAI 320 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| Comparison groups | Placebo v BAI 320 mcg/day |
|---|---|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0119 [46] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.149 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.265 |
| upper limit | -0.033 |

Notes:

[46] - Statistical significance is <=0.05.

| **Statistical analysis title** | Asthma Symptoms: Placebo to BAI 640 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| | |
|---|---|
| Comparison groups | Placebo v BAI 640 mcg/day |
| Number of subjects included in analysis | 212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0854 [47] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.102 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.217 |
| upper limit | 0.014 |

Notes:

[47] - Statistical significance is <=0.05.

| **Statistical analysis title** | Asthma Symptoms: Placebo to MDI 320 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 320 mcg/day |
| Number of subjects included in analysis | 212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0016 [48] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.189 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.306 |
| upper limit | -0.072 |

Notes:

[48] - Statistical significance is <=0.05.

| **Statistical analysis title** | Asthma Symptoms: Placebo to MDI 640 mcg/day |
|---|---|

Statistical analysis description:

LS means, difference of LS means and its 95% confidence interval, and p-value are obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week and treatment by week interaction.

| | |
|---|---|
| Comparison groups | Placebo v MDI 640 mcg/day |

| | |
|---|---|
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 [49] |
| Method | repeated measures mixed model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.216 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.332 |
| upper limit | -0.101 |

Notes:

[49] - Statistical significance is <=0.05.

## Secondary: Time to Withdrawal from the Study Treatment Due to Meeting Stopping Criteria for Worsening Asthma

| | |
|---|---|
| End point title | Time to Withdrawal from the Study Treatment Due to Meeting Stopping Criteria for Worsening Asthma |

End point description:

Time to withdrawal due to meeting stopping criteria is defined as number of days elapsed from the date of the first dose of double-blind study treatment to the date of withdrawal due to meeting stopping criteria. Stopping criteria are:
- FEV1 as measured at the study center is below the FEV1 stability limit value calculated at RV.
- Based upon review of patient diary data, the patient has experienced any of the following during any 7-day period:
  - 4+ days in which the highest (of 3 efforts) am PEF fall below the PEF stability limit calculated when randomized. The patient meets with the investigator who determines whether the FEV1 is consistent with worsening asthma;
  - 3+ days in which 12+ inhalations/day of rescue medication were used
  - 2+ days in which the patient experienced a nighttime asthma symptom score of more than 2
  - Clinical asthma exacerbation requiring (for example) the use of systemic corticosteroids, or the emergency room or hospitalization.

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

End point timeframe:

Day 1 – Week 12

| **End point values** | Placebo | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106[50] | 104[51] | 106[52] | 106[53] |
| Units: Days | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |

Notes:

[50] - Full analysis set
9999=not able to calculate as few patients met stopping criteria
[51] - Full analysis set
9999=not able to calculate as few patients met stopping criteria
[52] - Full analysis set
9999=not able to calculate as few patients met stopping criteria
[53] - Full analysis set
9999=not able to calculate as few patients met stopping criteria

| End point values | MDI 640 mcg/day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 107[54] | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | | | |

Notes:

[54] - Full analysis set
9999=not able to calculate as few patients met stopping criteria

### Statistical analyses

No statistical analyses for this end point

## Secondary: Participants with Adverse Events

| End point title | Participants with Adverse Events |
|---|---|

End point description:

An adverse event was defined in the protocol as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an inability to carry out usual activities. Relation of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes. Treatment-emergent AEs (TEAE) started during the treatment timeframe.

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

End point timeframe:

Day 1 to Week 13

| End point values | Placebo | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106[55] | 106[56] | 106[57] | 107[58] |
| Units: participants | | | | |
| At least 1 AE | 29 | 31 | 37 | 33 |
| At least 1 severe TEAE | 1 | 2 | 1 | 0 |
| At least 1 treatment-related TEAE | 2 | 5 | 16 | 6 |
| At least 1 serious AE | 0 | 1 | 1 | 1 |
| At least 1 AE causing discontinuation | 0 | 0 | 2 | 0 |

Notes:

[55] - Safety population

[56] - Safety population

[57] - Safety population

[58] - Safety population

| End point values | MDI 640 mcg/day | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 107[59] | | | |
| Units: participants | | | | |
| At least 1 AE | 45 | | | |

| | | | | |
|---|---|---|---|---|
| At least 1 severe TEAE | 2 | | | |
| At least 1 treatment-related TEAE | 13 | | | |
| At least 1 serious AE | 2 | | | |
| At least 1 AE causing discontinuation | 0 | | | |

Notes:

[59] - Safety population

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Day 1 to Week 13 | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

| Reporting groups | |
|---|---|
| Reporting group title | BAI 320 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |
| Reporting group title | BAI 640 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via breath actuated inhaler (BAI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |
| Reporting group title | MDI 320 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 40 mcg of beclomethasone dipropionate per inhalation delivered via metered-dose inhaler (MDI) (twice daily) totaling 320 mcg/day. Plus 4 inhalations of placebo breath-actuated inhaler (BAI) (twice daily) for 12 weeks. | |
| Reporting group title | MDI 640 mcg/day |
| Reporting group description: | |
| Patients took 4 inhalations of 80 mcg of beclomethasone dipropionate per inhalation delivered via metered dose inhaler (MDI) (twice daily) totaling 640 mcg/day. Plus 4 inhalations of placebo breath actuated inhaler (BAI) (twice daily) for 12 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients took 4 inhalations of matching placebo breath actuated inhaler (BAI) (twice daily) plus 4 inhalations of placebo metered dose inhaler (MDI) (twice daily) for 12 weeks. | |

| Serious adverse events | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 106 (0.94%) | 1 / 107 (0.93%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 106 (0.00%) | 1 / 107 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 106 (0.00%) | 1 / 107 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 106 (0.00%) | 1 / 107 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 106 (0.00%) | 0 / 107 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 106 (0.00%) | 1 / 107 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 106 (0.94%) | 0 / 107 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 106 (0.00%) | 0 / 107 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 106 (0.00%) | 0 / 107 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 106 (0.00%) | 0 / 107 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 106 (0.00%) | 0 / 107 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | MDI 640 mcg/day | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 106 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 0 / 106 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | BAI 320 mcg/day | BAI 640 mcg/day | MDI 320 mcg/day |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 106 (8.49%) | 11 / 106 (10.38%) | 9 / 107 (8.41%) |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Oral candidiasis | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 10 / 106 (9.43%) | 3 / 107 (2.80%) |
| occurrences (all) | 7 | 12 | 3 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 1 / 106 (0.94%) | 7 / 107 (6.54%) |
| occurrences (all) | 4 | 1 | 7 |

| **Non-serious adverse events** | MDI 640 mcg/day | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 107 (11.21%) | 2 / 106 (1.89%) | |
| Infections and infestations | | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 9 / 107 (8.41%) | 0 / 106 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 107 (3.74%) | 2 / 106 (1.89%) | |
| occurrences (all) | 4 | 2 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 April 2014 | Amendment 1 (dated 24 April 2014) to the protocol was issued after 140 patients were enrolled into the study.<br>The primary reasons for the amendment were removal of prohibited medications and clarification of study procedure. The following major procedural changes (not all-inclusive) were made to the protocol:<br>• Clarified minimum age requirements for certain countries where local regulations exclude participation by minors<br>• Specified, as part of inclusion criteria, that historical spirometry data need only include the expiratory tracings<br>• Edited allowed medications to include aqueous formulations of intranasal steroids and included nonsteroidal anti inflammatory drug use as standard of care<br>• Corrected minor discrepancies and made changed to wording in the protocol for added clarity. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported