



Clinical trial results:

A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group, 12-Week Clinical Study to Assess the Efficacy and Safety of 80 or 160 mcg/Day of Beclomethasone Dipropionate Delivered via Breath-Actuated Inhaler (BAI) or Metered-Dose Inhaler (MDI) in Pediatric Patients 4 Through 11 Years of Age with Persistent Asthma

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-004632-30 |
| Trial protocol | PL HR |
| Global end of trial date | 11 February 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 26 July 2018 |
| First version publication date | 26 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | BDB-AS-302 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02040766 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Teva Branded Pharmaceutical Products R&D |
| Sponsor organisation address | 41 Moores Road, Frazer, United States, 19355 |
| Public contact | Director, Clinical Research, MD, Teva Branded Pharmaceutical Products R&D, 001 888-483-8279, Info.era-clinical@teva.de |
| Scientific contact | Director, Clinical Research, MD, Teva Branded Pharmaceutical Products R&D, 001 888-483-8279, Info.era-clinical@teva.de |

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 | 01 August 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 February 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of beclomethasone dipropionate administered via breath-activated inhaler (BAI) and metered-dose inhaler (MDI) (80 or 160 mcg/day) compared with placebo treatment in pediatric patients 4 through 11 years of age with persistent asthma as assessed by the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) percent predicted forced expiratory volume in 1 second (FEV1) area under the effect curve from time 0 to 12 weeks (FEV1 AUEC 0-12wk).

Protection of trial subjects:

Written and/or oral information about the study was provided to all patients and their caregivers in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent/assent was obtained from each caregiver/patient before any study procedures or assessments were done. It was explained to the caregivers/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/assent form that was signed by the caregiver/patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the caregivers/patients.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 23 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 65 |
| Country: Number of subjects enrolled | Croatia: 7 |
| Country: Number of subjects enrolled | Mexico: 67 |
| Country: Number of subjects enrolled | Ukraine: 23 |
| Country: Number of subjects enrolled | United States: 466 |
| Worldwide total number of subjects | 628 |
| EEA total number of subjects | 72 |

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) | 628 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were screened at 123 centers in Croatia, Mexico, Poland, Ukraine, and the United States. The intent-to-treat (ITT) population included all randomly assigned patients

Pre-assignment

Screening details:

Patients were randomly assigned to treatment through a qualified randomization service provider. This system was used to ensure a balance across treatment groups, within each stratum.

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, Monitor, Data analyst |

Blinding implementation details:

Patients were randomly assigned to treatment through a qualified randomization service provider (ie, IRT). This system was used to ensure a balance across treatment groups, within each stratum (prior ICS therapy and prior NCS therapy groups).

To maintain the study blind there was no discernible difference between beclomethasone dipropionate and placebo within each configuration (BAI or MDI).

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo BAI and MDI |

Arm description:

Placebo was administered via breath-actuated inhaler (BAI) twice daily. Additionally placebo was administered via metered-dose inhaler (MDI) twice daily.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

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

Dosage and administration details:

Placebo was delivered by a single inhalation using a breath-actuated inhaler (BAI) twice each day.

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

Dosage and administration details:

Placebo was delivered by a single inhalation using a metered-dose inhaler (MDI) twice each day.

| | |
|--|------------------------------------|
| Investigational medicinal product name | albuterol/salbutamol 90 mcg |
| Investigational medicinal product code | |
| Other name | bronchodilators, Ventolin, ProAir® |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Rescue medication (albuterol/salbutamol hydrofluoroalkane (HFA) MDI [90 mcg ex-actuator] or equivalent) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the treatment period.

| | |
|------------------|----------------|
| Arm title | BDP 80 mcg BAI |
|------------------|----------------|

Arm description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (40 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Beclomethasone dipropionate BAI |
| Investigational medicinal product code | |
| Other name | BDP, breath-actuated inhaler |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Beclomethasone dipropionate (BDP), was delivered by a single inhalation using a breath-actuated inhaler (BAI) at levels of 40 mcg or 80 mcg per inhalation, twice each day.

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

Dosage and administration details:

Placebo was delivered by a single inhalation using a metered-dose inhaler (MDI) twice each day.

| | |
|--|------------------------------------|
| Investigational medicinal product name | albuterol/salbutamol 90 mcg |
| Investigational medicinal product code | |
| Other name | bronchodilators, Ventolin, ProAir® |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Rescue medication (albuterol/salbutamol hydrofluoroalkane (HFA) MDI [90 mcg ex-actuator] or equivalent) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the treatment period.

| | |
|------------------|-----------------|
| Arm title | BDP 160 mcg BAI |
|------------------|-----------------|

Arm description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (80 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Beclomethasone dipropionate BAI |
| Investigational medicinal product code | |
| Other name | BDP, breath-actuated inhaler |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

| | |
|--|------------------------------------|
| Dosage and administration details: | |
| Beclomethasone dipropionate (BDP), was delivered by a single inhalation using a breath-actuated inhaler (BAI) at levels of 40 mcg or 80 mcg per inhalation, twice each day. | |
| Investigational medicinal product name | Placebo MDI |
| Investigational medicinal product code | |
| Other name | metererd-dose inhaler |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo was delivered by a single inhalation using a metered-dose inhaler (MDI) twice each day. | |
| Investigational medicinal product name | albuterol/salbutamol 90 mcg |
| Investigational medicinal product code | |
| Other name | bronchodilators, Ventolin, ProAir® |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Rescue medication (albuterol/salbutamol hydrofluoroalkane (HFA) MDI [90 mcg ex-actuator] or equivalent) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the treatment period. | |
| Arm title | BDP 80 mcg MDI |
| Arm description: | |
| Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (40 mcg twice a day). | |
| Placebo BAI twice daily for blinding. | |
| Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Beclomethasone dipropionate MDI |
| Investigational medicinal product code | |
| Other name | BDP, metered-dose inhaler, QVAR® |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Beclomethasone dipropionate (BDP), was delivered by a single inhalation using a metered-dose inhaler (MDI) at levels of 40 mcg or 80 mcg per inhalation, twice each day. | |
| Investigational medicinal product name | Placebo BAI |
| Investigational medicinal product code | |
| Other name | breath-activated inhaler |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo was delivered by a single inhalation using a breath-actuated inhaler (BAI) twice each day. | |
| Investigational medicinal product name | albuterol/salbutamol 90 mcg |
| Investigational medicinal product code | |
| Other name | bronchodilators, Ventolin, ProAir® |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Rescue medication (albuterol/salbutamol hydrofluoroalkane (HFA) MDI [90 mcg ex-actuator] or equivalent) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the treatment period. | |
| Arm title | BDP 160 mcg MDI |

Arm description:

Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (80 mcg twice a day).

Placebo BAI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|--|----------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Beclomethasone dipropionate MDI |
| Investigational medicinal product code | |
| Other name | BDP, metered-dose inhaler, QVAR® |
| Pharmaceutical forms | Inhalation vapour, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Beclomethasone dipropionate (BDP), was delivered by a single inhalation using a metered-dose inhaler (MDI) at levels of 40 mcg or 80 mcg per inhalation, twice each day.

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

Dosage and administration details:

Placebo was delivered by a single inhalation using a breath-actuated inhaler (BAI) twice each day.

| | |
|--|------------------------------------|
| Investigational medicinal product name | albuterol/salbutamol 90 mcg |
| Investigational medicinal product code | |
| Other name | bronchodilators, Ventolin, ProAir® |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Rescue medication (albuterol/salbutamol hydrofluoroalkane (HFA) MDI [90 mcg ex-actuator] or equivalent) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the treatment period.

| Number of subjects in period 1 | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI |
|--------------------------------|---------------------|----------------|-----------------|
| Started | 127 | 126 | 125 |
| Completed | 109 | 116 | 113 |
| Not completed | 18 | 10 | 12 |
| Consent withdrawn by subject | 4 | 3 | 2 |
| Adverse event, non-fatal | 1 | 1 | 1 |
| Not reported | 1 | - | - |
| Non-compliance | - | 1 | - |
| Lost to follow-up | 4 | 1 | 3 |
| Lack of efficacy | 6 | 3 | 4 |
| Protocol deviation | 2 | 1 | 2 |

| Number of subjects in period 1 | BDP 80 mcg MDI | BDP 160 mcg MDI |
|--------------------------------|----------------|-----------------|
| Started | 125 | 125 |

| | | |
|------------------------------|-----|-----|
| Completed | 112 | 112 |
| Not completed | 13 | 13 |
| Consent withdrawn by subject | 3 | 2 |
| Adverse event, non-fatal | - | 2 |
| Not reported | - | - |
| Non-compliance | - | - |
| Lost to follow-up | 1 | 4 |
| Lack of efficacy | 6 | 5 |
| Protocol deviation | 3 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo BAI and MDI |
|-----------------------|---------------------|

Reporting group description:

Placebo was administered via breath-actuated inhaler (BAI) twice daily. Additionally placebo was administered via metered-dose inhaler (MDI) twice daily.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|----------------|
| Reporting group title | BDP 80 mcg BAI |
|-----------------------|----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (40 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|-----------------|
| Reporting group title | BDP 160 mcg BAI |
|-----------------------|-----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (80 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|----------------|
| Reporting group title | BDP 80 mcg MDI |
|-----------------------|----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (40 mcg twice a day).

Placebo BAI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|-----------------|
| Reporting group title | BDP 160 mcg MDI |
|-----------------------|-----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (80 mcg twice a day).

Placebo BAI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| Reporting group values | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI |
|--|---------------------|----------------|-----------------|
| Number of subjects | 127 | 126 | 125 |
| Age categorical | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 127 | 126 | 125 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |

| | | | |
|---|---------------|---------------|---------------|
| Age continuous Units: years arithmetic mean standard deviation | 8.2 ± 2.06 | 8.5 ± 2.10 | 8.4 ± 1.84 |
| Gender categorical Units: Subjects | | | |
| Female | 41 | 52 | 46 |
| Male | 86 | 74 | 79 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 4 | 4 |
| Asian | 0 | 2 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 42 | 34 | 33 |
| White | 71 | 69 | 69 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 11 | 17 | 17 |

| Reporting group values | BDP 80 mcg MDI | BDP 160 mcg MDI | Total |
|---|----------------|-----------------|-------|
| Number of subjects | 125 | 125 | 628 |
| Age categorical Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 125 | 125 | 628 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| Age continuous Units: years arithmetic mean standard deviation | 8.2 ± 1.78 | 8.4 ± 1.86 | - |
| Gender categorical Units: Subjects | | | |
| Female | 49 | 50 | 238 |
| Male | 76 | 75 | 390 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 1 | 15 |
| Asian | 0 | 0 | 4 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 37 | 49 | 195 |
| White | 76 | 63 | 348 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 9 | 12 | 66 |

End points

End points reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo BAI and MDI |
|-----------------------|---------------------|

Reporting group description:

Placebo was administered via breath-actuated inhaler (BAI) twice daily. Additionally placebo was administered via metered-dose inhaler (MDI) twice daily.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|----------------|
| Reporting group title | BDP 80 mcg BAI |
|-----------------------|----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (40 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|-----------------|
| Reporting group title | BDP 160 mcg BAI |
|-----------------------|-----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (80 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|----------------|
| Reporting group title | BDP 80 mcg MDI |
|-----------------------|----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (40 mcg twice a day).

Placebo BAI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|-----------------|
| Reporting group title | BDP 160 mcg MDI |
|-----------------------|-----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (80 mcg twice a day).

Placebo BAI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

Primary: Standardized Baseline-adjusted Trough Morning Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Area Under the Effect Curve From Time 0 to 12 Weeks (AUEC(0-12wk))

| | |
|-----------------|--|
| End point title | Standardized Baseline-adjusted Trough Morning Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Area Under the Effect Curve From Time 0 to 12 Weeks (AUEC(0-12wk)) |
|-----------------|--|

End point description:

Trough morning FEV1 measurements were taken pre-dose and pre-rescue bronchodilator treatment for asthma.

Baseline was defined as baseline trough morning percent predicted FEV1. 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 ('best attempt') FEV1 value from 3 acceptable and 2 repeatable maneuvers (maximum of 8 attempts) was used.

The full analysis set (FAS) included all patients in the ITT population who received at least 1 dose of study drug and had at least 1 post baseline trough morning (pre-dose and pre-rescue bronchodilator) assessment of percent predicted FEV1.

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

| End point values | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI | BDP 80 mcg MDI |
|-------------------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 113 ^[1] | 111 ^[2] | 116 ^[3] | 114 ^[4] |
| Units: liters | | | | |
| least squares mean (standard error) | 2.62 (± 0.744) | 5.43 (± 0.742) | 3.25 (± 0.732) | 3.54 (± 0.734) |

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

| End point values | BDP 160 mcg MDI | | | |
|-------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 114 ^[5] | | | |
| Units: liters | | | | |
| least squares mean (standard error) | 3.71 (± 0.734) | | | |

Notes:

[5] - FAS

Statistical analyses

| Statistical analysis title | % Pred FEV1 AUEC(0-12wk): 80 mcg BAI-Placebo |
|--|--|
| Statistical analysis description: | |
| ANCOVA model with effects due to baseline trough morning percent predicted FEV1, sex, age, current protocol-allowed asthma therapy (inhaled corticosteroid (ICS) or noncorticosteroid (NCS) therapy) at the time of screening visit, during the run-in period, and during treatment. | |
| Comparison groups | BDP 80 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 224 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0063 ^[6] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.796 |
| upper limit | 4.821 |

Notes:

[6] - significance of 0.05

| | |
|---|---|
| Statistical analysis title | % Pred FEV1 AUEC(0-12wk): 160 mcg BAI-Placebo |
| Statistical analysis description: ANCOVA model with effects due to baseline trough morning percent predicted FEV1, sex, age, current protocol-allowed asthma therapy (inhaled corticosteroid (ICS) or noncorticosteroid (NCS) therapy) at the time of screening visit, during the run-in period, and during treatment. | |
| Comparison groups | BDP 160 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5332 [7] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.354 |
| upper limit | 2.614 |

Notes:

[7] - significance of 0.05

| | |
|---|--|
| Statistical analysis title | % Pred FEV1 AUEC(0-12wk): 80 mcg MDI-Placebo |
| Statistical analysis description: ANCOVA model with effects due to baseline trough morning percent predicted FEV1, sex, age, current protocol-allowed asthma therapy (inhaled corticosteroid (ICS) or noncorticosteroid (NCS) therapy) at the time of screening visit, during the run-in period, and during treatment. | |
| Comparison groups | BDP 80 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3649 [8] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.077 |
| upper limit | 2.924 |

Notes:

[8] - significance of 0.05

| | |
|---|---|
| Statistical analysis title | % Pred FEV1 AUEC(0-12wk): 160 mcg MDI-Placebo |
| Statistical analysis description: ANCOVA model with effects due to baseline trough morning percent predicted FEV1, sex, age, current protocol-allowed asthma therapy (inhaled corticosteroid (ICS) or noncorticosteroid (NCS) therapy) at the time of screening visit, during the run-in period, and during treatment. | |
| Comparison groups | BDP 160 mcg MDI v Placebo BAI and MDI |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2823 ^[9] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.902 |
| upper limit | 3.088 |

Notes:

[9] - significance of 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:

The analysis of change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF calculated across the 12-week treatment period was performed using a mixed model for repeated measures (MMRM) with effects due to baseline weekly average of daily trough morning PEF.

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

End point timeframe:

Day 1 (baseline), weeks 1-12

| End point values | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI | BDP 80 mcg MDI |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 124 ^[10] | 124 ^[11] | 122 ^[12] | 121 ^[13] |
| Units: liters | | | | |
| least squares mean (standard error) | 4.3 (± 2.11) | 15.6 (± 2.08) | 12.8 (± 2.12) | 11.9 (± 2.11) |

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

| End point values | BDP 160 mcg MDI | | | |
|-------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 123 ^[14] | | | |
| Units: liters | | | | |
| least squares mean (standard error) | 10.8 (± 2.11) | | | |

Notes:

[14] - FAS

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | CFB Morning PEF: 80 mcg BAI-Placebo |
| Comparison groups | BDP 80 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 11.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.58 |
| upper limit | 17.06 |

| | |
|---|---------------------------------------|
| Statistical analysis title | CFB Morning PEF: 160 mcg BAI-Placebo |
| Comparison groups | BDP 160 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0041 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.71 |
| upper limit | 14.24 |

| | |
|---|--------------------------------------|
| Statistical analysis title | CFB Morning PEF: 80 mcg MDI-Placebo |
| Comparison groups | BDP 80 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 245 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0103 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 7.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.79 |
| upper limit | 13.35 |

| | |
|---|---------------------------------------|
| Statistical analysis title | CFB Morning PEF: 160 mcg MDI-Placebo |
| Comparison groups | BDP 160 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0278 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 6.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 12.23 |

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: | |
| The analysis of change from baseline in the weekly average of daily evening PEF across the 12-week treatment period was performed using a mixed model for repeated measures (MMRM) with effects due to baseline weekly average of daily evening PEF. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 (baseline), weeks 1-12 | |

| End point values | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI | BDP 80 mcg MDI |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 124 ^[15] | 124 ^[16] | 122 ^[17] | 121 ^[18] |
| Units: liters | | | | |
| least squares mean (standard error) | 1.4 (± 2.11) | 13.1 (± 2.09) | 11.4 (± 2.12) | 11.3 (± 2.12) |

Notes:

[15] - FAS

[16] - FAS

[17] - FAS

[18] - FAS

| End point values | BDP 160 mcg MDI | | | |
|-----------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 123 ^[19] | | | |
| Units: liters | | | | |

| | | | | |
|-------------------------------------|--------------------|--|--|--|
| least squares mean (standard error) | 10.1 (\pm 2.12) | | | |
|-------------------------------------|--------------------|--|--|--|

Notes:

[19] - FAS

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | CFB Evening PEF: 80 mcg BAI - Placebo |
| Comparison groups | BDP 80 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 11.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.96 |
| upper limit | 17.45 |

| | |
|---|--|
| Statistical analysis title | CFB Evening PEF: 160 mcg BAI - Placebo |
| Comparison groups | BDP 160 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0007 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 10 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.2 |
| upper limit | 15.76 |

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | CFB Evening PEF: 80 mcg MDI - Placebo |
| Comparison groups | BDP 80 mcg MDI v Placebo BAI and MDI |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 245 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 9.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.11 |
| upper limit | 15.68 |

| | |
|---|--|
| Statistical analysis title | CFB Evening PEF: 160 mcg MDI - Placebo |
| Comparison groups | BDP 160 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0031 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.95 |
| upper limit | 14.49 |

Secondary: Change From Baseline in the Weekly Average of Total Daily (24-hour) Use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations) Over Weeks 1-12

| | |
|--|--|
| End point title | Change From Baseline in the Weekly Average of Total Daily (24-hour) Use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations) Over Weeks 1-12 |
| End point description: The change from baseline in the weekly average of total daily (24-hour) use of albuterol/ salbutamol inhalation aerosol (number of inhalations) across the 12 weeks was analyzed using a mixed model for repeated measures (MMRM). | |
| End point type | Secondary |
| End point timeframe: Day 1 (baseline), weeks 1-12 | |

| End point values | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI | BDP 80 mcg MDI |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 124 ^[20] | 124 ^[21] | 122 ^[22] | 121 ^[23] |
| Units: number of inhalations | | | | |
| least squares mean (standard error) | -0.36 (± 0.069) | -0.72 (± 0.068) | -0.50 (± 0.069) | -0.41 (± 0.069) |

Notes:

[20] - FAS

[21] - FAS

[22] - FAS

[23] - FAS

| End point values | BDP 160 mcg MDI | | | |
|-------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 123 ^[24] | | | |
| Units: number of inhalations | | | | |
| least squares mean (standard error) | -0.54 (± 0.069) | | | |

Notes:

[24] - FAS

Statistical analyses

| Statistical analysis title | CFB Daily Use of Rescue Meds: 80 mcg BAI-Placebo |
|---|--|
| Comparison groups | BDP 80 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.548 |
| upper limit | -0.174 |

| Statistical analysis title | CFB Daily Use of Rescue Meds: 160 mcg BAI-Placebo |
|---|---|
| Comparison groups | BDP 160 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.132 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.331 |
| upper limit | 0.044 |

| | |
|---|--|
| Statistical analysis title | CFB Daily Use of Rescue Meds: 80 mcg MDI-Placebo |
| Comparison groups | BDP 80 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 245 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5866 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | 0.136 |

| | |
|---|---|
| Statistical analysis title | CFB Daily Use of Rescue Meds: 160 mcg MDI-Placebo |
| Comparison groups | BDP 160 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0587 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.369 |
| upper limit | 0.007 |

Secondary: Change From Baseline in the Weekly Average of the Total Daily Asthma Symptom Score Over Weeks 1-12

| | |
|-----------------|--|
| End point title | Change From Baseline in the Weekly Average of the Total Daily Asthma Symptom Score Over Weeks 1-12 |
|-----------------|--|

End point description:

The total daily asthma symptom score is the average of the daytime and nighttime scores analyzed using an mixed model for repeated measures (MMRM). Baseline was defined as the average of recorded morning and evening asthma symptom scores over the 7 days before randomization. Daytime Scores 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; Nighttime Scores range from 0=No symptoms during the night to 4=Symptoms so severe that I did not sleep at all. The daily asthma symptom score was therefore 0 - 9 with 0=no symptoms during the day or night and 9=severe symptoms both day and night.

| | |
|------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 (baseline), weeks 1-12 | |

| End point values | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI | BDP 80 mcg MDI |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 124 ^[25] | 124 ^[26] | 122 ^[27] | 121 ^[28] |
| Units: units on a scae | | | | |
| least squares mean (standard error) | -0.27 (± 0.036) | -0.44 (± 0.036) | -0.36 (± 0.036) | -0.31 (± 0.036) |

Notes:

[25] - FAS

[26] - FAS

[27] - FAS

[28] - FAS

| End point values | BDP 160 mcg MDI | | | |
|-------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 123 ^[29] | | | |
| Units: units on a scae | | | | |
| least squares mean (standard error) | -0.36 (± 0.036) | | | |

Notes:

[29] - FAS

Statistical analyses

| Statistical analysis title | Asthma Symptom Score: 80 mcg BAI-Placebo |
|---|--|
| Comparison groups | Placebo BAI and MDI v BDP 80 mcg BAI |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0011 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.261 |
| upper limit | -0.065 |

| Statistical analysis title | Asthma Symptom Score: 160 mcg BAI-Placebo |
|----------------------------|---|
|----------------------------|---|

| | |
|---|---------------------------------------|
| Comparison groups | BDP 160 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0869 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.185 |
| upper limit | 0.013 |

| | |
|---|--|
| Statistical analysis title | Asthma Symptom Score: 80 mcg MDI-Placebo |
| Comparison groups | BDP 80 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 245 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4388 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.138 |
| upper limit | 0.06 |

| | |
|---|---|
| Statistical analysis title | Asthma Symptom Score: 160 mcg MDI-Placebo |
| Comparison groups | BDP 160 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1041 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.18 |
| upper limit | 0.017 |

Secondary: Kaplan-Meier Estimates For Time to Withdrawal Due to Meeting Stopping Criteria for Worsening Asthma During the 12- week Treatment Period

| | |
|-----------------|--|
| End point title | Kaplan-Meier Estimates For Time to Withdrawal Due to Meeting Stopping Criteria for Worsening Asthma During the 12- week Treatment Period |
|-----------------|--|

End point description:

Time to withdrawal due to meeting stopping criteria was defined as number of days elapsed from the date of first dose of double-blind study treatment to the date of withdrawal due to meeting stopping criteria.

Kaplan-Meier estimates (median and 95% CI of the median) are not applicable if the proportion of participants withdrawn is less than 0.5.

Values of 9999 indicate the values could not be estimated because too few participants withdrew.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to 12 weeks | |

| End point values | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI | BDP 80 mcg MDI |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 124 ^[30] | 124 ^[31] | 122 ^[32] | 121 ^[33] |
| Units: days | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |

Notes:

[30] - FAS

[31] - FAS

[32] - FAS

[33] - FAS

| End point values | BDP 160 mcg MDI | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 123 ^[34] | | | |
| Units: days | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | | | |

Notes:

[34] - FAS

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Time to Withdrawal: 80 mcg BAI-Placebo |
| Comparison groups | BDP 80 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.287 |
| Method | Logrank |

| | |
|---|---|
| Statistical analysis title | Time to Withdrawal: 160 mcg BAI-Placebo |
| Comparison groups | BDP 160 mcg BAI v Placebo BAI and MDI |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5257 |
| Method | Logrank |

| | |
|---|--|
| Statistical analysis title | Time to Withdrawal: 80 mcg MDI-Placebo |
| Comparison groups | BDP 80 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 245 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9982 |
| Method | Logrank |

| | |
|---|---|
| Statistical analysis title | Time to Withdrawal: 160 mcg MDI-Placebo |
| Comparison groups | BDP 160 mcg MDI v Placebo BAI and MDI |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7633 |
| Method | Logrank |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind Study Treatment: Day 1 to Week 12

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo BAI and MDI |
|-----------------------|---------------------|

Reporting group description:

Placebo was administered via breath-actuated inhaler (BAI) twice daily. Additionally placebo was administered via metered-dose inhaler (MDI) twice daily.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|----------------|
| Reporting group title | BDP 80 mcg BAI |
|-----------------------|----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (40 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|-----------------|
| Reporting group title | BDP 160 mcg BAI |
|-----------------------|-----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a breath-actuated inhaler (BAI) twice daily (80 mcg twice a day).

Placebo MDI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|----------------|
| Reporting group title | BDP 80 mcg MDI |
|-----------------------|----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (40 mcg twice a day).

Placebo BAI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| | |
|-----------------------|-----------------|
| Reporting group title | BDP 160 mcg MDI |
|-----------------------|-----------------|

Reporting group description:

Beclomethasone dipropionate (BDP) was administered via a metered-dose inhaler (MDI) twice daily (80 mcg twice a day).

Placebo BAI twice daily for blinding.

Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) at 90 mcg ex-actuator) or equivalent was used as rescue medication throughout the study.

| Serious adverse events | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI |
|---|---------------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| Serious adverse events | BDP 80 mcg MDI | BDP 160 mcg MDI | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 0 / 125 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Placebo BAI and MDI | BDP 80 mcg BAI | BDP 160 mcg BAI |
|---|---------------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 127 (6.30%) | 6 / 126 (4.76%) | 13 / 125 (10.40%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 127 (3.15%) | 1 / 126 (0.79%) | 3 / 125 (2.40%) |
| occurrences (all) | 7 | 1 | 3 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 127 (3.15%) | 5 / 126 (3.97%) | 11 / 125 (8.80%) |
| occurrences (all) | 5 | 6 | 14 |

| Non-serious adverse events | BDP 80 mcg MDI | BDP 160 mcg MDI | |
|---|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 125 (12.00%) | 11 / 125 (8.80%) | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 9 / 125 (7.20%) | 6 / 125 (4.80%) | |
| occurrences (all) | 11 | 7 | |
| Infections and infestations | | | |

| | | | |
|---|----------------------|----------------------|--|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 125 (4.80%) 7 | 6 / 125 (4.80%) 7 | |
|---|----------------------|----------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 21 May 2014 | <p>Amendment 1 (dated 21 May 2014) to the protocol was issued after 49 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The primary reasons for the amendment were modification of prohibited medications and clarification of study procedures. The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none">• At the prescreening visit, dose of fluticasone propionate MDI adjusted from 88 mcg/day to 176 mcg/day to be consistent with ICS of combination therapy.• Changes to allow nebulizer treatment reversibility testing as standard of care and to clarify that historical spirometry data need only include the expiratory tracings.• Edited to allow PRN use of low-potency topical corticosteroids and aspirin use as standard of care, revised to indicate that aqueous formulations of intranasal steroids are allowable before SV but aerosol formulations are disallowed, clarified when ocular steroid use is permitted, removed tricyclic antidepressants as a prohibited medication, and added medicinal marijuana and inhaled nicotine to the list of prohibited medication. |
| 18 December 2014 | <p>Amendment 2 (dated 18 December 2014) to the protocol was issued after 220 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The primary reasons for the amendment were the change in the primary efficacy variable, lowering of the minimum age for eligibility to participate in the study, the addition of the option to rescreen patients who failed to qualify for the study based on spirometry criteria, and permission of younger patients who were unable to perform spirometry to participate in the study on the basis of PEF criteria in place of spirometry criteria. The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none">• The minimum age requirement for participation in the study was changed from 5 to 4 years of age.• A change in the primary efficacy measure at endpoint. The primary efficacy variable was changed to standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) percent predicted FEV1 AUEC(0-12wk) after discussions with the Food and Drug Administration indicated a concern over handling of missing data due to early dropouts.• The order of secondary objectives was changed to correspond with a change in the order of statistical testing of the secondary variables.• The number of attempts to perform acceptable and repeatable spirometry was increased from 5 to 8 and the option to rescreen patients who failed screening based on spirometry was added because younger patients were having difficulty performing spirometry measurements adequately.• Inclusion criterion C was changed to allow patients aged 4 to 5 years to participate in the study using PEF measurements. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28710850>