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) andmetered-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	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 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	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 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
Protocol deviation	2	1	2
Lack of efficacy	6	3	4

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
Protocol deviation	3	-
Lack of efficacy	6	5

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	8.2	8.5	8.4
standard deviation	± 2.06	± 2.10	± 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	8.2	8.4	
standard deviation	± 1.78	± 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 (± 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	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: • 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	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: • 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