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

Summary

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

Results information

Result version number	v2
This version publication date	17 July 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set Data were reversed, some data were missing, corrections were made

Trial information

Trial identification

Sponsor protocol code	BDB-AS-301

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc. , 1 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc. , 1 215-591-3000, ustevatrials@tevapharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 July 2015
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	02 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 415
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Hungary: 40

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	26
Adults (18-64 years)	457
From 65 to 84 years	48
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	BAI 320 mcg/day

Arm description:

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

Arm type	Experimental

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	BAI 640 mcg/day

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	MDI 320 mcg/day

Arm description:

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

Arm type	Active comparator

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	MDI 640 mcg/day

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

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

Baseline characteristics

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

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

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

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

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

End points

End points reporting groups

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

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

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

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

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

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

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

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

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

Notes:

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

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

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

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

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

Notes:

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

Statistical analyses

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

Statistical analysis description:

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

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

Notes:

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

[7] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

FEV1, sex, age, and treatment.

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

Notes:

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

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

Statistical analysis description:

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

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

Notes:

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

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

Statistical analysis description:

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

Comparison groups	Placebo v MDI 640 mcg/day

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

Notes:

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

[13] - Statistical significance is <=0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[14] - Full analysis set

[15] - Full analysis set

[16] - Full analysis set

[17] - Full analysis set

End point values	MDI 640 mcg/day			

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

Notes:

[18] - Full analysis set

Statistical analyses

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

Statistical analysis description:

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

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

Notes:

[19] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[20] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[21] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[22] - Statistical significance is <=0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[23] - Full analysis set

[24] - Full analysis set

[25] - Full analysis set

[26] - Full analysis set

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

Notes:

[27] - Full analysis set

Statistical analyses

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

Statistical analysis description:

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

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

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

Notes:

[28] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[29] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[30] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[31] - Statistical significance is <=0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[32] - Full analysis set

[33] - Full analysis set

[34] - Full analysis set

[35] - Full analysis set

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

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

Notes:

[36] - Full analysis set

Statistical analyses

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

Statistical analysis description:

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

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

Notes:

[37] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[38] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[39] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[40] - Statistical significance is <=0.05.

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[41] - Full analysis set

[42] - Full analysis set

[43] - Full analysis set

[44] - Full analysis set

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

Notes:

[45] - Full analysis set

Statistical analyses

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

Statistical analysis description:

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

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

Notes:

[46] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[47] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

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

Notes:

[48] - Statistical significance is <=0.05.

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

Statistical analysis description:

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

Comparison groups	Placebo v MDI 640 mcg/day

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

Notes:

[49] - Statistical significance is <=0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Day 1 – Week 12

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

Notes:

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Adverse Events

End point title	Participants with Adverse Events

End point description:

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

End point type	Secondary

End point timeframe:

Day 1 to Week 13

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

Notes:

[55] - Safety population

[56] - Safety population

[57] - Safety population

[58] - Safety population

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

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

Notes:

[59] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Ask Pat	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

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

Serious adverse events	BAI 320 mcg/day	Placebo	MDI 640 mcg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 106 (0.94%)	0 / 106 (0.00%)	2 / 107 (1.87%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Gastric disorder			
subjects affected / exposed	0 / 106 (0.00%)	0 / 106 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

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

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

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

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pharyngeal abscess			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BAI 320 mcg/day	Placebo	MDI 640 mcg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 106 (8.49%)	2 / 106 (1.89%)	12 / 107 (11.21%)
Infections and infestations			

Oral candidiasis			
subjects affected / exposed	5 / 106 (4.72%)	0 / 106 (0.00%)	9 / 107 (8.41%)
occurrences (all)	7	0	11
Upper respiratory tract infection			
subjects affected / exposed	4 / 106 (3.77%)	2 / 106 (1.89%)	4 / 107 (3.74%)
occurrences (all)	4	2	4

Non-serious adverse events	BAI 640 mcg/day	MDI 320 mcg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 106 (10.38%)	9 / 107 (8.41%)	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	10 / 106 (9.43%)	3 / 107 (2.80%)	
occurrences (all)	12	3	
Upper respiratory tract infection			
subjects affected / exposed	1 / 106 (0.94%)	7 / 107 (6.54%)	
occurrences (all)	1	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported