Clinical trial results:
A Phase 2, double-blind, randomized, parallel-group, placebo-controlled, multicenter study, comparing budesonide pMDI 160 g bid with placebo: a
6-week efficacy and safety study in children aged 6 to <12 years with asthma

Summary

EudraCT number	2010-018315-15
Trial protocol	SK LV HU PL BG
Global end of trial date	23 September 2013

Results information

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

Trial information

Trial identification

Sponsor protocol code	D589GC00001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	AstraZeneca R&D, SE-431 83 Mölndal, Sweden,
Public contact	Göran Eckerwall, MD, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Göran Eckerwall, MD, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2013
Global end of trial reached?	Yes
Global end of trial date	23 September 2013
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 determine the efficacy of budesonide pMDI 160 µg bid (80 µg x 2 inhalations bid) as a single ingredient product over a 6-week period in children aged 6 to <12 years who demonstrated the need for ICS controller therapy.

Protection of trial subjects:

An Independent Ethics Committee/Institutional Review Board approved the final clinical study protocol, including the final version of the Informed Consent Form and Child Assent Forms and any other written information and/or materials, to be provided to the patients in accordance with national regulations. The investigator ensured the distribution of these documents to the applicable IEC/IRB, and to the study site staff.

The principal investigator at each center ensured that both the patient (assent) and the parent or legal guardian (consent) were given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients were notified that they were free to withdraw from the study at any time. The patient was given the opportunity to ask questions and allowed time to consider the information provided.

The patient’s signed and dated informed assent and the parent or legal guardian’s consent were obtained and documented before conducting any study procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Hungary: 112
Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	United States: 110
Worldwide total number of subjects	304
EEA total number of subjects	183

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)	304
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:

This multicenter study was conducted in Bulgaria, Hungary, Latvia, Poland, Slovakia, South Africa, and the United States between 07 August 2011 and 05 April 2013.

Pre-assignment

Screening details:

The study consisted of a screening visit (Visit 1), an enrollment visit (Visit 2), a 7- to 21-day run-in/qualification period, a randomization visit (Visit 3), and 6 further weekly visits during a treatment period of 6 weeks. A telephone follow-up was conducted approximately 2 weeks after the final study visit.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo pMDI bid

Arm type	Placebo
Investigational medicinal product name	Placebo pMDI bid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations bid

Arm title	Budesonide

Arm description:

Budesonide pMDI 160 mcg bid

Arm type	Experimental
Investigational medicinal product name	Budesonide pMDI 160 µg bid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

80 µg x 2 inhalations bid

Number of subjects in period 1	Placebo	Budesonide
Started	152	152
Completed	92	121
Not completed	60	31
Consent withdrawn by subject	4	1
Other reasons	8	5
Study-Specific Withdrawal Criteria	48	25

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo pMDI bid	
Reporting group title	Budesonide
Reporting group description: Budesonide pMDI 160 mcg bid	

Reporting group values	Placebo	Budesonide	Total
Number of subjects	152	152	304
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	152	152	304
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	9	9	
standard deviation	± 1.62	± 1.63	-
Gender, Male/Female Units: participants			
Female	58	54	112
Male	94	98	192
Age group (<8, >=8 years) Units: Subjects			
<8 years	33	33	66
>= 8 years	119	119	238

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo pMDI bid	
Reporting group title	Budesonide
Reporting group description: Budesonide pMDI 160 mcg bid	

Primary: Change in morning peak expiratory flow (PEF) from baseline to the treatment period average

End point title	Change in morning peak expiratory flow (PEF) from baseline to the treatment period average
End point description: The peak expiratory flow rate is the maximal rate that a person can exhale during a short maximal expiratory effort after a full inspiration. Baseline was calculated using the mean of the data recorded during the last 7 days of the run-in period, and the treatment period average was calculated as the mean of all available data recorded during the entire treatment period.	
End point type	Primary
End point timeframe: Baseline to 6 weeks	

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	151		
Units: liters/minute				
least squares mean (standard error)	4.1 (± 3.19)	17.8 (± 3.24)		

Statistical analyses

Statistical analysis title	Morning PEF
Statistical analysis description: Change from baseline to treatment period average was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.	
Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	13.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	19.7
Variability estimate	Standard error of the mean
Dispersion value	3.1

Notes:

[1] - To address multiplicity, a step-down procedure was used. If the treatment difference for the primary variable, morning PEF, was statistically significant ($p<0.05$), then the key secondary variable, FEV1, was tested at the 0.05 level of significance.

Secondary: Change in Forced expiratory volume in 1 second (FEV1) from baseline to treatment period average

End point title	Change in Forced expiratory volume in 1 second (FEV1) from baseline to treatment period average

End point description:

FEV1 is the volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity. Baseline was defined as the pre-dose assessment value measured at randomization (Visit 3), and the treatment period average was calculated as the mean of all available data recorded during the entire treatment period.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	152		
Units: liters				
least squares mean (standard error)	0 (± 0.023)	0.06 (± 0.023)		

Statistical analyses

Statistical analysis title	FEV1

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[2] - To address multiplicity, a step-down procedure was used. If the treatment difference for the primary variable, morning PEF, was statistically significant ($p<0.05$), then the key secondary variable, FEV1, was tested at the 0.05 level of significance.

Secondary: Change in evening PEF from baseline to the treatment period average

End point title	Change in evening PEF from baseline to the treatment period average

End point description:

The peak expiratory flow rate is the maximal rate that a person can exhale during a short maximal expiratory effort after a full inspiration. Baseline was calculated using the mean of the data recorded during the last 7 days of the run-in period, and the treatment period average was calculated as the mean of all available data recorded during the entire treatment period.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	151		
Units: liters/minute				
least squares mean (standard error)	4 (± 3.08)	14.7 (± 3.13)		

Statistical analyses

Statistical analysis title	Evening PEF

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	10.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.9
upper limit	16.7
Variability estimate	Standard error of the mean
Dispersion value	3

Secondary: Change in forced vital capacity (FVC) from baseline to treatment period average

End point title	Change in forced vital capacity (FVC) from baseline to treatment period average

End point description:

FVC is the total volume of air expired after a full inspiration. Baseline was defined as the pre-dose assessment value measured at randomization (Visit 3), and the treatment period average was calculated as the mean of all available data recorded during the entire treatment period.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	152		
Units: liters				
least squares mean (standard error)	0 (± 0.021)	0.04 (± 0.021)		

Statistical analyses

Statistical analysis title	FVC

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0673
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.08

Variability estimate	Standard error of the mean
Dispersion value	0.02

Secondary: Change in forced mid-expiratory flow between 25% and 75% of the FVC (FEF25-75) from baseline to treatment period average

End point title	Change in forced mid-expiratory flow between 25% and 75% of the FVC (FEF25-75) from baseline to treatment period average

End point description:

FEF25-75 is the average rate of airflow during the midportion of the forced vital capacity. Baseline was defined as the pre-dose assessment value measured at randomization (Visit 3), and the treatment period average was calculated as the mean of all available data recorded during the entire treatment period.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	152		
Units: liters/second				
least squares mean (standard error)	0.01 (± 0.045)	0.11 (± 0.045)		

Statistical analyses

Statistical analysis title	FEF25-75

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0216
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.044

Secondary: Change in total daily and daytime asthma symptom scores from baseline to treatment period average

End point title	Change in total daily and daytime asthma symptom scores from baseline to treatment period average

End point description:

Patients, with the help of their caregiver, were required to rate and document their asthma symptoms twice daily as an overall symptom score for the time period since their previous recording. The following rating scales were used: 0 = None; no symptoms of asthma; 1 = Mild symptoms; awareness of asthma symptoms and/or signs that are easily tolerated; 2 = Moderate symptoms, asthma symptoms with some discomfort, causing some interference with daily activities or sleep; 3 = Severe symptoms; incapacitating asthma symptoms and/or signs, with inability to perform daily activities or to sleep.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	152		
Units: units on a scale				
least squares mean (standard error)				
Daytime asthma symptom score	-0.2 (± 0.06)	-0.4 (± 0.06)		
Total asthma symptom score	-0.5 (± 0.11)	-0.8 (± 0.11)		

Statistical analyses

Statistical analysis title	Daytime asthma symptom scores

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [3]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[3] - Analysis for change in daytime asthma symptom score from baseline to treatment period average.

Statistical analysis title	Total daily asthma symptom scores

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 [4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[4] - Analysis for change in total asthma symptom score from baseline to treatment period average.

Secondary: Change in nighttime asthma symptom score from baseline to treatment period average

End point title	Change in nighttime asthma symptom score from baseline to treatment period average

End point description:

Patients, with the help of their caregiver, were required to rate and document their asthma symptoms twice daily as an overall symptom score for the time period since their previous recording. The following rating scales were used: 0 = None; no symptoms of asthma; 1 = Mild symptoms; awareness of asthma symptoms and/or signs that are easily tolerated; 2 = Moderate symptoms, asthma symptoms with some discomfort, causing some interference with daily activities or sleep; 3 = Severe symptoms; incapacitating asthma symptoms and/or signs, with inability to perform daily activities or to sleep.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	152		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.06)	-0.4 (± 0.06)		

Statistical analyses

Statistical analysis title	Nighttime asthma symptom scores

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0079
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.06

Secondary: Change in nighttime awakenings and nighttime awakenings with reliever medication use from baseline to treatment period average

End point title	Change in nighttime awakenings and nighttime awakenings with reliever medication use from baseline to treatment period average

End point description:

Patients, with the help of their caregiver, were asked to respond to a standard question each morning as they completed their eDiary. The question to be answered was, "Did your asthma cause you to wake-up last night?" If yes, patients were asked, "Did you need to use your reliever medication (albuterol/salbutamol inhaler) before you went back to sleep?" Baseline is defined as the percentage of days where patient experienced nighttime awakenings out of all available days where data was collected during the last 7 days of the run-in period.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	152		
Units: percentage of days with awakenings				
least squares mean (standard error)				
Nighttime awakenings	-9.8 (± 1.81)	-14.5 (± 1.84)		
Nighttime awakenings with reliever use	-6.1 (± 1.17)	-10 (± 1.18)		

Statistical analyses

Statistical analysis title	Awakenings (%)

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0095 [5]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	1.78

Notes:

[5] - Analysis for change in nighttime awakenings from baseline to treatment period average.

Statistical analysis title	Awakenings with reliever use (%)

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [6]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	1.15

Notes:

[6] - Analysis for change in nighttime awakenings with reliever medication use from baseline to treatment period average.

Secondary: Change in total daily and daytime reliever medication use from baseline to treatment period average

End point title	Change in total daily and daytime reliever medication use from baseline to treatment period average

End point description:

The patient, with the help of their caregiver, recorded the number of inhalations of reliever medication used, for relief of asthma symptoms, twice daily in the eDiary. Patients were asked to respond to a standard question twice daily (morning and evening). The question to be answered was, "How many albuterol/salbutamol inhalations since last diary entry?"

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	152		
Units: inhalations per day				
least squares mean (standard error)				
Daytime reliever medication use	-0.1 (± 0.07)	-0.4 (± 0.07)		
Total reliever medication use	-0.3 (± 0.11)	-0.7 (± 0.11)		

Statistical analyses

Statistical analysis title	Daytime reliever use (inh/day)

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[7] - Analysis for change in daytime reliever medication use from baseline to treatment period average.

Statistical analysis title	Total reliever use (inh/day)

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[8] - Analysis for change in total reliever medication use from baseline to treatment period average.

Secondary: Change in nighttime reliever medication use from baseline to treatment period average

End point title	Change in nighttime reliever medication use from baseline to treatment period average

End point description:

The patient, with the help of their caregiver, recorded the number of inhalations of reliever medication used, for relief of asthma symptoms, twice daily in the eDiary. Patients were asked to respond to a standard question twice daily (morning and evening). The question to be answered was, "How many albuterol/salbutamol inhalations since last diary entry?"

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	152		
Units: inhalations per day				
least squares mean (standard error)	-0.1 (± 0.06)	-0.4 (± 0.06)		

Statistical analyses

Statistical analysis title	Nightime reliever use (inh/day)

Statistical analysis description:

Change from baseline to treatment period average was analyzed using an ANCOVA model with terms for treatment, age group (<8 years and ≥8 years of age) and country with baseline as a covariate.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.06

Secondary: Number of withdrawals due to pre-defined asthma events

End point title	Number of withdrawals due to pre-defined asthma events

End point description:

Patients were considered to have experienced a "pre-defined asthma event" if any of the following conditions were met during the study: 1. At each visit or follow-up visit, a decrease in morning pre-dose FEV1 >=20% from the Visit 3 (randomization visit) morning pre-dose FEV1 or a decrease to <65% of predicted normal value; 2. The use of >=8 actuations of albuterol/salbutamol per day on 3 or more days within any period of 7 consecutive days following randomization; 3. A decrease in morning PEF >=20% from baseline on 3 or more days within any period of 7 consecutive days after randomization; 4. Two or more nights with an awakening due to asthma, which required the use of reliever medication within any period of 7 consecutive days after randomization; 5. A clinical exacerbation requiring emergency treatment, hospitalization, or use of an asthma medication not allowed by the study protocol.

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Placebo	Budesonide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	152		
Units: participants	50	25		

Statistical analyses

Statistical analysis title	Time to withdrawal due to asthma event

Statistical analysis description:

Log rank test for time to withdrawal due to predefined asthma event.

Comparison groups	Placebo v Budesonide
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from enrollment (Visit 2) throughout the treatment period and included the 2-week follow-up period (last contact by telephone).

Adverse event reporting additional description:

Only AEs starting on or after the first dose and <=1 day after last dose are included in the summaries below.

A total of 153 patients reported non-serious adverse events; 64 on Budesonide pMDI 160mcg b.i.d, 89 on Placebo pMDI b.i.d. Numbers for non-serious AEs in the reporting group table are based on the 2.5% threshold frequency.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Placebo pMDI b.i.d.
Reporting group description: -	
Reporting group title	Budesonide pMDI 160mcg b.i.d.

Reporting group description: -

Serious adverse events	Placebo pMDI b.i.d.	Budesonide pMDI 160mcg b.i.d.	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 152 (0.00%)	0 / 152 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo pMDI b.i.d.	Budesonide pMDI 160mcg b.i.d.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 152 (30.26%)	29 / 152 (19.08%)	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	11 / 152 (7.24%)	1 / 152 (0.66%)	
occurrences (all)	11	1	
OROPHARYNGEAL PAIN			

subjects affected / exposed	4 / 152 (2.63%)	3 / 152 (1.97%)	
occurrences (all)	4	3	
Epistaxis			
subjects affected / exposed	3 / 152 (1.97%)	1 / 152 (0.66%)	
occurrences (all)	3	1	
Cough			
subjects affected / exposed	3 / 152 (1.97%)	0 / 152 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
INFLUENZA			
subjects affected / exposed	4 / 152 (2.63%)	4 / 152 (2.63%)	
occurrences (all)	5	5	
NASOPHARYNGITIS			
subjects affected / exposed	9 / 152 (5.92%)	12 / 152 (7.89%)	
occurrences (all)	11	12	
PHARYNGITIS			
subjects affected / exposed	8 / 152 (5.26%)	5 / 152 (3.29%)	
occurrences (all)	8	5	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 152 (5.26%)	3 / 152 (1.97%)	
occurrences (all)	9	3	
Sinusitis			
subjects affected / exposed	3 / 152 (1.97%)	1 / 152 (0.66%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2010	The entry criteria stating that reversibility of FEV1 of ≥15% from prealbuterol/salbutamol level within 15 to 30 minutes after administration of a standard dose of albuterol/salbutamol was updated to ≥12%. It was also stated that only 1 attempt at reversibility would be allowed. The instruction that prophylactic or regularly scheduled use of study reliever medications was not allowed in this study was updated to state that prophylactic or regularly scheduled use of these medications should be avoided.
27 September 2010	The use of nasal steroids was further restricted to prohibit initiation of nasal steroid treatment, titration of dose, and change of dosing frequency during the study.
22 June 2011	Within the patient population targeted for recruitment, FEV1 and/or FEV1 reversibility vary over time. Allowing 2 opportunities for patients to demonstrate a pre-bronchodilator morning clinic FEV1 within the specified range and to demonstrate reversibility of FEV1 of ≥12% was expected to enhance recruitment without changing the characterization of the study patient population or jeopardizing patient safety.
30 November 2011	The purpose of the amendment was to increase the probability of successful patient screening and randomization into the study and to increase the probability of patients who were randomized to complete the treatment period without impacting the characterization of the patient population being studied.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported