AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide pMDI
Study Code	D589GC00001
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A Phase 2, double-blind, randomized, parallel-group, placebo-controlled, multicenter study, comparing budesonide pMDI 160 µg bid with placebo: a 6-week efficacy and safety study in children aged 6 to <12 years with asthma

Study dates: First subject enrolled: 07 August 2011
Last subject last visit: 05 April 2013

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

Of the 101 study centers selected for this study, 72 randomized patients into the study. This study was conducted in the following countries: Bulgaria, Hungary, Latvia, Poland, Slovakia, South Africa, and the United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the efficacy of budesonide pressurized metered dose inhaler (pMDI) 160 µg twice a day (80 µg x 2 inhalations twice a day) as a single ingredient product over a 6-week period in children aged 6 to <12 years who demonstrate the need for inhaled glucocorticosteroid (ICS) controller therapy.	Primary: Change from baseline in morning PEF
Secondary	Efficacy	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 demonstrate the need for ICS controller therapy by evaluating in-clinic morning pre-dose FEV_1.	Key Secondary: Change from baseline in in-clinic morning FEV_1
			Change from baseline in spirometry values (FVC and FEF_{25-75})
			Change from baseline in evening PEF
			Change from baseline in asthma symptom scores (nighttime, daytime, and total)
			Change from baseline in nighttime awakenings due to asthma symptoms (overall and where reliever medication is used).
			Change from baseline in use of reliever medication (nighttime, daytime, and total)
			Number of withdrawals due to pre-defined criteria for worsening of asthma and time to first event.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Safety	Safety	To compare the safety of budesonide pMDI to placebo pMDI	AEs, discontinuations due to AEs, SAEs, physical examination, vital signs.
Exploratory	Efficacy		Change from baseline in morning FEV_1 from patient diary
			Change from baseline in evening FEV_1 from patient diary

AE adverse event; CSP Clinical study protocol; FEF_{25-75} Forced mid-expiratory flow between 25% and 75% of the forced vital capacity; FEV_1 Forced expiratory volume in 1 second; FVC Forced vital capacity; ICS inhaled glucocorticosteroid; PEF Peak expiratory flow; pMDI pressurized metered dose inhaler; SAE serious adverse event.

Study design

This was a 6 week, randomized, double-blind, parallel-group, placebo-controlled, multicenter, Phase 2 efficacy and safety study comparing inhaled budesonide 160 µg bid (as 80 µg pMDI x 2 actuations) with placebo in pediatric patients with asthma aged 6 to <12 years who demonstrated the need for inhaled glucocorticosteroid (ICS) controller therapy. The primary outcome was change of pre-dose morning peak expiratory flow (PEF) from baseline.

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 to check for possible adverse events (AEs) since the final study visit. In addition, this study included a robust asthma safety plan with conservative criteria for pre-defined asthma events mandating withdrawal.

Target subject population and sample size

Male and female pediatric patients (aged 6 to <12 years) who had a documented clinical diagnosis of asthma as defined by the American Thoracic Society (ATS) for at least 6 months prior to Visit 1 that required either daily low dose range ICS therapy (as defined by 2007 National Asthma Education and Prevention Program [NAEPP] guidelines) or daily therapy with a leukotriene receptor antagonist (LTRA) as monotherapy for at least 30 days prior to Visit 2. To be eligible to participate in the study, patients had to demonstrate reversibility of FEV_1 of ≥12% to a short acting β_2-agonist (or have a documented reversibility history within the last 12 months) and met asthma symptom and lung function criteria during a placebo run-in/qualification period.

It was proposed to randomize 290 patients in order to obtain 266 patients (133 per treatment group) with evaluable data for the primary and key secondary efficacy endpoints.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Budesonide pMDI 160 µg (taken as budesonide pMDI 80 µg/actuation x 2 inhalations), or matching placebo pMDI (x 2 inhalations), taken twice daily, in the morning and evening, via oral inhalation. Individual batch numbers and further information are included in the clinical study report (CSR) appendix.

Duration of treatment

The duration of treatment was 6 weeks, preceded by a run-in/qualification period of 7 to 21 days and followed by telephone contact 2 weeks after the final visit.

Statistical methods

The primary efficacy variable in this study was the change in morning PEF from baseline (mean of last 7 days of run-in period) to the treatment period average (ie, average of the available data in the treatment period). This was analyzed with an analysis of covariance (ANCOVA) model with terms for treatment, age group (<8 years and ≥8 years of age), and country and with baseline morning PEF as a covariate. In addition, analysis was performed on the patient's change from baseline to their average value at the end of treatment (average of the last 7 available treatment days).

The key secondary efficacy variable was the change from baseline (latest available pre-dose value) to the treatment period average for FEV_1 and this was analyzed in a similar way to morning PEF. In addition, analysis was performed on the patient's change from baseline to end of treatment value. A sensitivity analysis based on LOCF was also performed. FVC and FEF_{25-75} were analyzed in a similar manner.

Multiplicity for the primary and key secondary variables was addressed using a step-down procedure. If the treatment difference for the primary efficacy variable is statistically significant at the 0.05 level then the key secondary variable will also be tested at this level.

Other secondary efficacy diary variables included evening PEF, reliever medication use (daytime, nighttime, and total), percentage of nights with awakenings due to asthma symptoms (overall and with reliever medication use) and asthma symptom scores (daytime, nighttime, and total). These individual diary variables were analyzed in the same way as morning PEF.

Time to the first pre-defined asthma event and time to withdrawal due to a pre-defined asthma event were described using Kaplan-Meier plots. The main statistical comparison between treatment groups was accomplished via a log-rank test.

Morning and evening FEV_1 from patient diary were exploratory variables and were analyzed in the same way as morning PEF.

All statistical comparisons were based on a 2-sided test using an alpha (α) level of significance of 5%. Nominal p-values were reported for all variables other than the primary and key secondary variables.

No formal hypothesis testing of safety data was planned, although treatment differences for certain variables were described with relative risks and associated 95% confidence intervals from statistical analyses.

Subject population

A total of 1361 patients were enrolled for possible study participation. Of these, 520 patients (38.2%) completed the enrollment visit and received run-in medication, 304 patients (22.3%) were randomized to investigational product, and 213 (70.1%) completed the study. A total of 91 patients (29.9%) who received treatment withdrew from the study. The most common reason for withdrawal from the study was development of study-specific withdrawal criteria (73 patients; 24.0% overall).

The majority of the randomized patients were White (88.8%), and the mean age of patients was 9.0 years of age (ranging from 6 to 11 years of age). Most patients (78.3%) were ≥8 years of age. The patient population recruited to the study was representative of the target study population of pediatric patients with asthma who need inhaled glucocorticosteroid (ICS) controller therapy.

Summary of efficacy results

Primary efficacy

Table S 2 ANCOVA Summary – Morning PEF Results (L/min) (Efficacy Analysis Set)

		Change within Group		Treatment Difference (Budesonide-Placebo)			
Change from baseline to:	**Treatment Group**	**LS Mean**	**SE**	**LS Mean**	**SE**	**95% CI**	**p-value**
Treatment Period Average [a]	Placebo pMDI bid (n = 151)	4.1	3.19	13.6	3.10	(7.5, 19.7)	<0.0001
	Budesonide pMDI 160 mcg bid (n = 151)	17.8	3.24				

[a] Treatment Period Average is defined as the mean value across all available on-treatment days.
Change from baseline to endpoint is analysed 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.
Baseline is defined as the mean of the last 7 available days of the run-in period.
E1002005 (Placebo) and E1870002 (Budesonide) have no morning and evening PEF or FEV_1 captured in the eDiary.
n=number of patients in the analysis set with data available for the analysis.

Budesonide pMDI was superior to placebo in improving morning PEF from baseline to treatment period average. The least squares (LS) mean change in morning PEF from baseline to treatment period average was 17.8 L/min for the budesonide pMDI group and 4.1 L/min for the placebo group. The treatment effect (13.6 L/min) was in favor of budesonide pMDI and was statistically significant (p<0.0001).

Key Secondary efficacy

Table S 3 ANCOVA Summary – FEV_1 Results (L) from Clinic Visits (Efficacy Analysis Set)

Change from baseline to:	Treatment Group	Change within Group		Treatment Difference (Budesonide-Placebo)			
		LS Mean	SE	LS Mean	SE	95% CI	p-value
Treatment Period Average [a]	Placebo pMDI bid (n = 149)	0.00	0.023	0.06	0.022	(0.02, 0.11)	0.0047
	Budesonide pMDI 160 mcg bid (n = 152)	0.06	0.023				

[a] Treatment Period Average is defined as the mean value across all available on-treatment visits.
Change from baseline to endpoint is analysed 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.
Baseline is defined as the latest non-missing assessment prior to first dose (typically Visit 3, Randomization).
E1700006, E1861042 and E1870001 (all Placebo) have no post-baseline spirometry data.
No baseline values are carried forwards.
n=number of patients in the analysis set with data available for the analysis.

Budesonide pMDI was superior to placebo in improving FEV_1 from baseline to treatment period average. The mean change in FEV_1 from baseline to treatment period average was 0.06 L for the budesonide pMDI group and 0.00 L for the placebo group. The treatment effect (0.06 L) was in favor of budesonide pMDI and was statistically significant (p=0.0047).

Other secondary efficacy variables

For all secondary variables, differences between the budesonide group and the placebo group were in favor of budesonide, and with the exception of FVC, these differences were nominally statistically significant. These variables included:

- measures of lung function (evening PEF [p=0.0004], in-clinic pre-dose FEF_{25-75} [p=0.0216], in-clinic pre-dose FVC [p=0.0673]),
- symptoms (daytime [p=0.0004], nighttime [p=0.0079], and total daily [p=0.0015], asthma symptom scores, nighttime awakenings due to asthma symptoms [p=0.0095], nighttime awakenings where reliever medication was used [p=0.0007]),

- reliever medication use (daytime [p=0.0001], nighttime [p<0.0001], and total [p<0.0001]),

- withdrawals due to pre-defined asthma events (p=0.0004).

Overall, analyses of primary and secondary efficacy variables showed that aerosolized budesonide pMDI 160 µg bid (80 µg x 2 inhalations bid), administered via the pMDI device over 6 weeks, demonstrated superior efficacy to placebo in asthmatic children aged 6 to <12 years who need ICS controller therapy.

Summary of safety results

In this study, aerosolized budesonide pMDI 160 µg bid (80 µg x 2 inhalations bid) via the pMDI device was safe and generally well-tolerated in asthmatic children aged 6 to <12 years who need ICS controller therapy, as evidenced by the following:

- There were no SAEs or deaths reported during the study.

- Vital sign and physical examination findings did not raise any safety concerns.

- Fewer AEs were reported by patients receiving budesonide pMDI compared with placebo, particularly regarding asthma-related AEs.

- Fewer patients receiving budesonide pMDI discontinued study treatment due to AEs compared with patients receiving placebo.