AstraZeneca

Drug product:	Symbicort® Turbuhaler®	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
Document No.:	CR-SD-039-0714		
Edition No.:	01		
Study code:	SD-039-0714		
Date:	22 September 2003		

Efficacy and safety of budesonide/formoterol Turbuhaler® (160/4.5 μg b.i.d. delivered dose) compared to budesonide Turbuhaler® (200 μg b.i.d. metered dose) in steroid-using asthmatic adolescent patients. A double-blind, double-dummy, randomised, parallel group, phase III, multicentre study. (ATTAIN STUDY)

Study centre(s)

This study was conducted at 122 centres in the United Kingdom: 119 general practice centres and 3 hospital centres. It was planned to conduct the study at approximately 80 general practice and hospital centres in the UK with 4-12 patients recruited from each centre.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	1 August 2001	Therapeutic confirmatory (III)
Last patient completed	6 September 2002	

Objectives

The primary objective of the study was to compare the efficacy of budesonide/formoterol Turbuhaler® (160/4.5 μg delivered dose b.i.d.) with budesonide Turbuhaler® (200 μg metered dose b.i.d.) in asthmatic adolescent patients over a 12-week treatment period by assessment of morning peak expiratory flow (mPEF L/min). Secondary efficacy variables were symptom free days, asthma control days, daytime and night-time asthma symptom scores, evening peak expiratory flow (ePEF), short-acting β_2 agonist (SAB_2) usage and nights with awakenings due

to asthma symptoms and health related quality of life scores (HRQL). The symptom variable of primary interest for the determination of the effect on asthma symptoms was symptom free days.

A secondary objective of the study was the safety of budesonide/formoterol Turbuhaler in terms of adverse events.

Study design

This study was designed as a double-blind, randomised, parallel group, multicentre study to determine the efficacy and safety of budesonide/formoterol Turbuhaler (320/9 μg daily delivered dose) in a single inhaler, compared to monotreatment with budesonide Turbuhaler (400 μg daily metered dose) in the treatment of inhaled steroid-using asthmatic symptomatic adolescent patients.

During the two week run-in period, patients received 200 μg (metered dose) budesonide Turbuhaler one inhalation twice daily instead of their regular inhaled glucocorticosteroid (iGCS). At the end of the run-in period, patients with asthma symptoms were randomised to budesonide/formoterol Turbuhaler 160/4.5 μg (delivered dose), one inhalation twice daily or budesonide Turbuhaler® 200 μg (metered dose), one inhalation twice daily for 12 weeks. Patients attended the clinic after 4, 8 and 12 weeks of treatment.

Target patient population and sample size

Male or female patients aged 12-17 years old, receiving an iGCS for perennial asthma, dose of iGCS within or equal to 375-1000 μg daily dose within the licensed dose for the patients' age, baseline FEV_1 values of 40-90% of predicted normal, demonstration of airway reversibility (≥12%) and experiencing asthma symptoms.

A sample size of 150 in each group was estimated to have 90% power to detect a difference in mean change in mPEF of 15 L/min assuming that the common standard deviation was 40 L/min and using a two group t-test with a 5% two-sided significance level.

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

Symbicort® (budesonide/formoterol) Turbuhaler 160/4.5 μg delivered dose, one inhalation twice daily. Batch numbers: P6299, P6334 and P6437

Pulmicort® (budesonide) Turbuhaler 200 μg metered dose, one inhalation twice daily. Batch numbers: P6298, P6331 and P6435

Placebo to budesonide/formoterol Turbuhaler, one inhalation twice daily. Batch numbers: P6301, P6333 and P6438

Placebo to budesonide Turbuhaler, one inhalation twice daily. Batch numbers: P6305, P6332 and P6436

Bricanyl® (terbutaline sulphate) Turbuhaler 0.5 mg metered dose, as required for rescue medication and for the reversibility test. Batch numbers: P6302, P6439, P6302 and P6384

Powder for inhalation 0.5 mg/dose (metered dose)

All investigational products were manufactured by AstraZeneca Liquid Production, Södertälje, Sweden.

During the run-in period, all patients discontinued use of their current inhaled steroid and were treated with Pulmicort Turbuhaler (budesonide) 200 μg metered dose, one inhalation twice daily.

Duration of treatment

The run-in period was 2 weeks and the randomised treatment period was 12 weeks.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: mPEF as recorded daily by patients in diary
- Secondary variables: Secondary variables were symptom free days, asthma control days, day time and night time asthma symptom scores, ePEF, SAB_2 usage and night time awakenings as recorded on diary cards and quality of life scores as recorded at clinic visits. The symptom variable of primary interest for the determination of the effect on asthma symptoms was symptom free days. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) assessed at clinic visits were also assessed.

Safety

Safety was assessed by the incidence of adverse events.

Statistical methods

The statistical analysis was based on the intention to treat (ITT) population. The change from baseline (average of last 10 days of run-in) to the treatment period (average of the whole treatment period) in the primary variable, morning PEF, was analysed using an analysis of covariance (ANCOVA) model with treatment and centre as fixed factors and the baseline value as a covariate. Secondary diary card variables, including derived variables symptom free days and asthma control days, HRQL, FEV_1 and FVC were compared between the treatments in an analysis similar to the one for the primary variable. All hypothesis testing was performed using two-sided alternatives. P-values less than 5% were considered statistically significant.

Adverse events were analysed by means of descriptive statistics and qualitative analysis.

Patient population

In total, 453 patients entered the run-in period and 271 patients from 122 centres were randomised to treatment (136 to budesonide/formoterol and 135 to budesonide). The mean age of adolescent patients was 14.1 years and they had a mean reversibility of 23.4% prior to randomisation. The majority of patients (79.9%) had suffered from asthma for more than 5 years. The patient population and disposition is given in Table S1.

Table S1 Patient population and disposition

		Budesonide/Formoterol		Budesonide		Total	
Population							
N randomised (N planned)		136	(150)	135	(150)	271	(300)
Demographic characteristics (safety set)							
Sex (n and % of patients)	Male	80	(58.8)	75	(56.0)	155	(57.4)
	Female	56	(41.2)	59	(44.0)	115	(42.6)
Age (years)	Mean (SD)	14.2	(1.7)	14.0	(1.6)	14.1	(1.6)
	Range	12 to 17		11 to 17		11 to 17	
Race (n and % of patients)	Caucasian	135	(99.3)	128	(95.5)	263	(97.4)
	Oriental	0	(0)	1	(0.7)	1	(0.4)
	Other	1	(0.7)	5	(3.7)	6	(2.2)
Baseline characteristics (ITT set)							
Pre-study treatment	BDP	79	(59.4)	74	(56.5)	153	(58.0)
(n and % of patients)[a]	Fluticasone	10	(7.5)	10	(7.6)	20	(7.6)
	Budesonide	42	(31.6)	46	(35.1)	88	(33.3)
	Seretide	3	(2.3)	1	(0.8)	4	(1.5)
Morning PEF (L/min)	Mean (SD)	403.2	(77.8)	389.1	(71.1)	396.2	(74.7)
	Range	183 to 571		256 to 591		183 to 591	
FEV_1 (% predicted normal)	N	131		129		260	
	Mean (SD)	73.4	(11.1)	76.4	(12.0)	74.9	(11.6)
	Range	39 to 90		50 to 129		39 to 129	
Disposition							
N (%) of patients who	Completed	111	(81.6)	108	(80.0)	219	(80.8)
	Discontinued	25	(18.4)	27	(20.0)	52	(19.2)
N analysed for safety[b]		136		134		270	
N analysed for efficacy (ITT)		133		131		264	

[a] One patient (00166) took both Seretide® and Budesonide during the same time period prior to the study and is included on the counts for both types of pre-study treatment.

[b] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

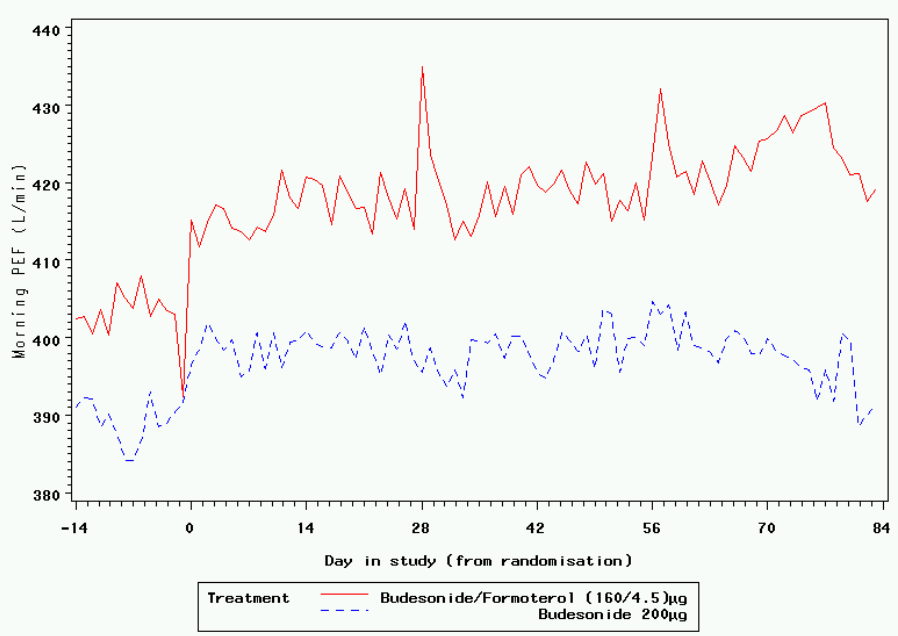
ITT=Intention to treat; N=Number

The treatment groups were generally well balanced in demographic and baseline characteristics. The mean mPEF, ePEF and reversibility were all slightly higher in the budesonide/formoterol group than in the budesonide group. The main reasons for discontinuation in both treatment groups after randomisation were 'eligibility criteria not fulfilled' and 'other'; the most common other reasons were patient randomised in error and poor/non-compliance.

Efficacy results

Both treatment groups showed an improvement in mPEF from baseline (Figure S1). The mPEF values for the budesonide/formoterol group were numerically higher at baseline than for the budesonide alone group, although this was adjusted for in the statistical analysis. Patients in the budesonide/formoterol group showed an adjusted increase in mPEF from baseline of 14.9 L/min. Patients on budesonide alone showed an adjusted increase of 10.2 L/min. Although the mPEF in the budesonide/formoterol group was numerically greater, there was no significant difference between the treatment groups with regard to the average change in mPEF from baseline to treatment (adjusted mean difference: 4.8 L/min, p=0.286, ANCOVA analysis).

Figure S1 Average morning PEF (L/min) by treatment, ITT analysis set



Results for the secondary variables obtained from diary card data (change from baseline to treatment period in symptom free days, ePEF, asthma symptom scores, SAB_2 usage, night-time awakenings and asthma control days) supported those of the primary variable. Both treatment groups showed an improvement from baseline, but there were no significant differences between the treatments in any of these secondary variables.

There was a significant difference between treatment groups in FEV_1 lung function assessed at clinic visits. Patients treated with budesonide/formoterol showed a significantly greater improvement in FEV_1 (average 0.13 L, p=0.01, ANCOVA analysis) than patients treated with budesonide.

Quality of Life results

There was no significant difference between treatment groups in the change from baseline to treatment period for the AQLQ(S)≥12 years domain and overall scores. Patients in the budesonide/formoterol group showed an adjusted increase from baseline of 0.24 in the overall score compared to an increase of 0.23 with budesonide alone. The baseline values for all 4 domains and overall score were very high and there was little scope for improvement during the randomised treatment period.

Safety results

A summary of adverse events in each category is presented in Table S2. The incidence and nature of adverse events associated with both treatments was similar. There was a low incidence of serious adverse events (SAEs) with only 2 SAEs (budesonide/formoterol: overdose; budesonide: bronchospasm) reported, which were both assessed as not related to treatment. The incidence of discontinuation due to adverse event (DAE) was 6% (8/134) in the budesonide treatment group and 2.9% (4/136) in the budesonide/formoterol group. The main reason for DAE during the study was deterioration of asthma (preferred term: asthma aggravated). No other significant AEs were identified during this study. Most of the AEs were of mild to moderate intensity. Nine patients (budesonide/formoterol: 3 patients, budesonide: 6 patients) experienced AEs of a severe intensity.

Table S2 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of Adverse Event	Budesonide/Formoterol (n=136)	Budesonide (n=134)
Any Adverse Event[a]	66 (49.3%)	65 (48.5%)
Serious Adverse Events[a]		
Serious adverse events leading to death[a]	0	0
Serious adverse events not leading to death[a]	1 (0.7%)	1 (0.7%)
Discontinuation of study treatment due to adverse events[a]	4 (2.9%)	8 (6.0%)
Any adverse events causally related to study treatment[a]	4 (2.9%)	3 (2.2%)
Any adverse events[b]	98	115
Serious adverse events[b]	1	1

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of these categories.

[b] Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 frequency of the event is counted.

The most common adverse events, as summarised by preferred term, are shown in Table S3. Respiratory infection and pharyngitis were the most common adverse events in both treatment groups.

Table S3 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (Preferred Term)	Budesonide/ Formoterol (n=136)	Budesonide (n=134)
Respiratory infection	20 (14.7%)	28 (20.9%)
Pharyngitis	6 (4.4%)	9 (6.7%)

[a] Events with a total frequency of ≥5% across all treatment groups are included in this table.

Changes in physical findings were small and showed no treatment-related trends.