AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	Budesonide/formoterol
Study Code	D5897C00004
Edition Number	1
Date	17 June 2008

A 4-week, open-label, randomized, multi-centre, parallel-group study evaluating the safety and efficacy of 4 actuations Symbicort® (budesonide/formoterol) HFA pMDI 40/2.25 µg twice daily, with and without spacer, in children (6-11 years) with asthma

Study dates: First patient enrolled: 19 September 2007
Last patient completed: 22 February 2008

Phase of development: Therapeutic confirmatory (III)

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

Study centres

The study was conducted in Poland, Hungary and Russia and patients were recruited from totally 12 centres. Of these, 7 were in Poland, 3 were in Hungary, and the remaining 2 in Russia.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to show that Symbicort pMDI 40/2.25 µg (delivered dose), 4 actuations twice daily (bid) with spacer has a similar systemic steroid potency as Symbicort pMDI 40/2.25 µg, 4 actuations bid in children with asthma.

The secondary objectives of the study were to compare the clinical efficacy and safety of Symbicort pMDI 40/2.25 µg, 4 actuations bid with or without spacer in children with asthma.

Study design

This was an open-label, randomised, multi-centre study with two parallel groups. The patients received Symbicort pressurized metered dose inhaler (pMDI) (budesonide/formoterol) 40/2.25 µg 4 actuations bid with or without spacer (AeroChamber Plus, valved holding chamber (VHC)) during a 4-week treatment period.

Target population and sample size

The target population consisted of children aged 6 to 11 years with persistent asthma previously receiving maintenance treatment with inhaled corticosteroids, peak expiratory flow (PEF) ≥50%, and with demonstrated symptoms during run-in.

It was estimated that 50 patients per treatment group would give a power of 80% to detect a true difference of about 50% in urinary free cortisol (UFC) levels. This was based on a residual standard deviation of 0.7 on the logarithmic scale, 2-sided test and a significance level of 5%. Alternatively, the precision of the study would be such that the 95% confidence interval for the ratio of treatment effects would extend from 76% of the estimated ratio to 132% of the estimated ratio.

The sample size calculation was made with a descriptive comparison of 2 treatments in mind, not for a formal establishment of equivalence. The confidence interval mentioned above should not be interpreted as equivalence limits. It is merely a way to express the expected precision of the treatment comparison.

Investigational product and comparators: dosage, mode of administration and batch numbers

Run-in maintenance medication: Pulmicort pMDI (budesonide). Dosage: 100 µg per actuation (metered dose), 2 actuations bid by inhalation for 11 to 17 days

Investigational product: Symbicort pMDI (budesonide/formoterol) with spacer (AeroChamber Plus VHC). Five batches (E05155-002L03, E05155-001L05, E05155-001L06, E05155-003L01 and E05155-003L02) of Symbicort pMDI were used in this study group. Two of these batches were also used in the comparator group. Dosage: 40 /2.25 µg per actuation (delivered dose) 4 actuations bid by inhalation

Comparator: Symbicort pMDI without spacer. Five batches (E05155-002L04, E05155-001L07, E05155-001L08, E05155-003L01, E05155-003L02) of Symbicort pMDI were used in this study group. Dosage: 40 /2.25 µg per actuation (delivered dose), 4 actuations bid by inhalation

Medication for the post-bronchodilatory assessment: Bricanyl Turbuhaler (terbutaline sulphate). Dosage: 0.5 mg/inhalation, 2 inhalations

Duration of treatment

After a 2-week run-in period, the patients were treated for 4 weeks with either Symbicort pMDI with spacer or Symbicort pMDI without spacer.

Criteria for evaluation - efficacy (main variables)

Primary variable (pharmacodynamic):

- 24-hour UFC excretion

Secondary efficacy variables:

- Forced expiratory volume in 1 second (FEV_1)
- Morning peak expiratory flow
- Evening peak expiratory flow
- Night-time awakenings due to asthma symptoms
- Use of reliever medication

Patient reported outcomes (PROs)

- Asthma symptoms day and night

Criteria for evaluation - safety (main variables)

Safety variables:

- Nature, incidence and severity of adverse events (AEs)
- Vital signs (pulse and blood pressure)

- Physical examination
- Urinalysis (dip-stick)

Statistical methods

Primary variable

Levels of UFC at end of treatment were expressed as a percentage of the level at baseline and subjected to analysis of covariance (ANCOVA) following a log-transformation. The ANCOVA model included fixed factors for treatment and country, and the logarithm of the baseline UFC level was used as a covariate. The ratio of treatment effects was obtained from the result of the ANCOVA and expressed as a percentage. A 95% confidence interval for the ratio was also calculated along with a p-value for the difference between treatments. According to the Statistical analysis plan (SAP), an analysis of the primary variable excluding erroneously included patients was made as a check of the stability of the results.

Secondary variables

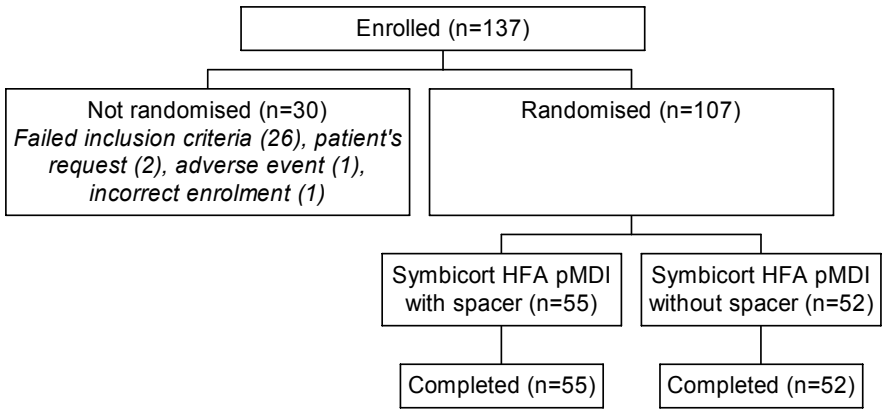
Changes in FEV_1 (expressed in L and as percent of predicted normal) from baseline (Visit 3) to the mean value of Visit 4 and Visit 5 were analysed. For PEF and other electronic diary (eDiary) variables, changes from baseline, the average during the last 10 days before Visit 3 to the average of the whole treatment period, were analysed. ANCOVA was used with treatment and country as fixed factors, and with the baseline value as a covariate. Treatment differences were estimated from the model and confidence intervals of 95% confidence level were calculated.

All tests were two-sided and p-values less than or equal to 0.05 were considered statistically significant.

Subject population

The disposition of the patients in this study is presented in Figure S1.

Figure S1 Study Flow Chart



The treatment groups were well matched at baseline, except for lung function, which was better in the Symbicort pMDI without spacer group (Table S1). There was a higher number of boys than girls, which is often seen in asthma studies in children. The 2 treatment groups were balanced with regard to sex. The usage of concomitant medication was reasonable in the clinical context. The obtained sample is representative for the intended study population. The study included enough patients to fulfil the aim in the power calculation.

Table S1 Treatment group comparison of demographic and disease data

		Symbicort pMDI with spacer	Symbicort pMDI	All
		n=55	n=52	n=107
Sex	Male	34	30	64
	Female	21	22	43
Age (years)	Mean	8.6	8.9	8.8
	Range	6-11	6-11	6-11
Race	White	55	52	107
Height (cm)	Mean	136.1	138.1	137.1
	Range	114-170	109-159	109-170
Time since diagnosis (years)	Median	3.00	3.55	3.20
	Range	0.4-9.0	0.6-8.7	0.4-9.0
Inhaled GCS at entry dose (µg)	n	55	52	107
	Mean	444.2	437.6	441.0
	Range	400-800	375-800	375-800
FEV_1 (L)	Mean	1.670	1.768	1.718
	Range	0.85-3.09	0.94-3.15	0.85-3.15
FEV_1 (% P.N.)	Mean	87.1	90.8	88.9
	Range	57-116	58-126	57-126
PEF morning (L/min)	Mean	215.4	236.0	225.4
	Range	107-349	156-363	107-363
PEF morning (% P.N.)	Mean	74.7	80.2	77.4
	Range	55-101	61-130	55-130
Asthma symptom score, day (0-3)	Mean	0.917	1.037	0.976
	Range	0.18-1.87	0.25-2.07	0.18-2.07
Asthma symptom score, night (0-3)	Mean	0.828	0.921	0.873

Table S1 Treatment group comparison of demographic and disease data

		Symbicort pMDI with spacer	Symbicort pMDI	All
		n=55	n=52	n=107
Total rescue use (inhalations/day)	Range	0.00-1.79	0.08-2.00	0.00-2.00
	Mean	0.89	0.67	0.78
	Range	0.0-4.0	0.0-5.0	0.0-5.0

For categorical data, frequencies are given; and for other data, mean values and ranges are given

Summary of efficacy results

The relative decrease in U-cortisol in the Symbicort pMDI with spacer group was 6.4% and the relative increase in the Symbicort pMDI without spacer group 7.6%. The estimated ratio was 0.870, ie 13% lower for Symbicort pMDI with spacer than for Symbicort pMDI without spacer (Table S2).

Table S2 Statistical analysis of relative change in 24-hour U-cortisol

Treatment	Geometric mean ratio (adjusted)	95% confidence interval	p-value
Symbicort pMDI with spacer	0.936	(0.797, 1.099)	
Symbicort pMDI	1.076	(0.916, 1.264)	
Ratio	0.870	(0.713, 1.061)	0.1666

ANCOVA adjusted for baseline and country.

There was a marked increase in mean morning and evening PEF in both treatment groups, with a corresponding improvement in symptom variables and use of rescue medication. There was a statistically significantly greater improvement in mean evening PEF in the Symbicort pMDI with spacer group compared with the Symbicort pMDI without spacer group (Table S3), with a similar but not statistically significant difference between groups for morning PEF. There was no evidence of any difference between treatment groups for asthma symptoms, awakenings, or use of rescue medication.

Table S3 Treatment comparisons for eDiary card variables

Variable	Treatment	Mean diff.	95% Confidence interval	p-value
PEF (L/min)				
-morning	Symbicort pMDI with spacer vs. Symbicort pMDI	8.09	(-1.20, 17.4)	0.087

Table S3 Treatment comparisons for eDiary card variables

Variable	Treatment	Mean diff.	95% Confidence interval	p-value
-evening	Symbicort pMDI with spacer vs. Symbicort pMDI	9.58	(0.560, 18.6)	0.038
Asthma symptoms				
-night-time score (0-3)	Symbicort pMDI with spacer vs. Symbicort pMDI	-0.005	(-0.153, 0.143)	0.945
-daytime score (0-3)	Symbicort pMDI with spacer vs. Symbicort pMDI	-0.001	(-0.151, 0.148)	0.987
-awakenings (%)	Symbicort pMDI with spacer vs. Symbicort pMDI	-1.41	(-9.34, 6.51)	0.724
Use of rescue medication				
-total no. of inhalations	Symbicort pMDI with spacer vs. Symbicort pMDI	-0.008	(-0.266, 0.251)	0.954
-night-time	Symbicort pMDI with spacer vs. Symbicort pMDI	0.026	(-0.104, 0.157)	0.692
-daytime	Symbicort pMDI with spacer vs. Symbicort pMDI	-0.028	(-0.166, 0.111)	0.694

ANCOVA adjusted for baseline and country.

Summary of safety results

No deaths, serious AEs (SAEs), or premature discontinuation of treatment with investigational product due to an AE (DAEs) were reported. The distribution of adverse events across treatment groups was unremarkable (see Table S4). Other safety monitoring (vital signs and urinalysis) showed no clinically important differences between treatment groups.

Table S4 Adverse events by preferred term

Preferred term	Symbicort pMDI with spacer n=55	Symbicort pMDI n=52	All n=107
Nasopharyngitis	0	2 (4%)	2 (2%)
Headache	1 (2%)	1 (2%)	2 (2%)
Viral upper respiratory tract infection	0	2 (4%)	2 (2%)
Urinary tract infection	1 (2%)	0	1 (1%)
Rhinitis	1 (2%)	0	1 (1%)

Table S4 Adverse events by preferred term

Preferred term	Symbicort pMDI with spacer n=55	Symbicort pMDI n=52	All n=107
Nocturia	1 (2%)	0	1 (1%)
Diarrhoea	0	1 (2%)	1 (1%)
Influenza	0	1 (2%)	1 (1%)
Cough	1 (2%)	0	1 (1%)
Dysphonia	0	1 (2%)	1 (1%)
Bronchitis	0	1 (2%)	1 (1%)
Vertigo	1 (2%)	0	1 (1%)
Abdominal pain upper	0	1 (2%)	1 (1%)