AstraZeneca

Drug product:	Symbicort pMDI	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Budesonide/formoterol		
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A 12-week randomised, double-blind, parallel-group, multicentre phase-III study to compare the efficacy and safety of Symbicort® pMDI (budesonide/formoterol 80/4.5 µg 2 actuations b.i.d., delivered dose) with that of Pulmicort® pMDI (budesonide 100 µg 2 actuations b.i.d., metered dose) and Symbicort Turbuhaler® (budesonide/formoterol 80/4.5 µg 2 actuations b.i.d., delivered dose) in children with asthma

Study centre(s)

This study was a multicentre study conducted in Argentina (4 centres), Brazil (6 centres), Denmark (14 centres), Hong Kong (1 centre), Mexico (6 centres), Poland (4 centres), Slovakia (12 centres), and Taiwan (6 centres).

Publications

None at the time of writing this report.

Study dates:

First subject enrolled	26 June, 2002
Last subject completed	16 May, 2003

Phase of Development

Therapeutic confirmatory (III)

Objectives

The *primary objective* of the study was to show that Symbicort® pressurised metered dose inhaler (pMDI) 80/4.5 µg 2 actuations twice daily (b.i.d.) was more efficacious than Pulmicort® pMDI 100 µg 2 actuations b.i.d. over a 12-week treatment period in children with asthma.

The *secondary objectives* of the study were:

1. To compare the efficacy of Symbicort pMDI 80/4.5 µg 2 actuations b.i.d. with that of Symbicort Turbuhaler® 80/4.5 µg 2 inhalations b.i.d. over a 12-week treatment period in children with asthma.
2. To investigate the safety profile of Symbicort pMDI 80/4.5 µg 2 actuations b.i.d., Symbicort Turbuhaler 80/4.5 µg 2 inhalations b.i.d., and Pulmicort pMDI 100 µg 2 actuations b.i.d. over a 12-week treatment period in children with asthma.

Study design

This was a multinational and multicentre study with a randomised, double-blinded, active-controlled, parallel-group design, starting with a 2-week run-in period which was followed by a 12-week treatment period comparing the efficacy and safety of Symbicort pMDI with that of Pulmicort pMDI (CFC; chlorofluorocarbon) and Symbicort Turbuhaler in the treatment of children with asthma.

Target subject population and sample size

Out-patients (6-11 years) of either sex with asthma and a history of clinically important exercise-induced bronchoconstriction, daily using 375-1000 µg of inhaled glucocorticosteroids (GCSs), and with a peak expiratory flow (PEF) ≥50% of predicted normal value (prebronchodilator). The subjects had to have a total asthma-symptom score (night-time plus daytime) ≥1 on at least 4 of the last 7 days of the run-in period and a mean morning PEF (mPEF) during the last 7 days of the run-in period of 50-85% of postbronchodilatory PEF, measured at Visit 1 (enrolment).

About 800 subjects were to be enrolled, whereof approximately 540 needed to be randomised in order to reach 450 evaluable subjects after 12 weeks (150 in each treatment arm) for having a 90% chance of detecting a true difference in mean change in mPEF of 11.3 L/min between treatments. This is based on an assumed standard deviation of 30 L/min, using a two-group t-test with a 5% two-sided significance level.

For the secondary objective, the lower and upper limits of the 95% confidence interval for the difference in mPEF between Symbicort pMDI and Symbicort Turbuhaler was compared with the equivalence limits -15L/min and 15L/min. Assuming a standard deviation of 30 L/min, there would be 90% probability for this confidence interval to be contained with the equivalence limits given that the actual difference was less than 3.5 L/min.

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

Symbicort pMDI (budesonide/formoterol) 80/4.5 µg (delivered dose) 2 actuations b.i.d. in aerosol form (batch nos. P6038, P6501/A, P6186, P6254, P6349). The propellant used in Symbicort pMDI is the hydrofluoroalkane (HFA) 227.

Pulmicort pMDI (budesonide) 100 µg (metered dose) 2 actuations b.i.d. in aerosol form (batch no. P6354, P6358). The propellant in Pulmicort pMDI are CFCs 11, 12, and 114. A 100 µg metered dose of Pulmicort corresponds to 80 µg delivered dose of the budesonide component in Symbicort.

Symbicort Turbuhaler (budesonide/formoterol) 80/4.5 µg (delivered dose) 2 inhalations b.i.d. in dry-powder form (batch nos. CL 19, CM 14, CC 18, CD 12)

Doses were given in a double-dummy way owing to the difference in appearance of the devices.

Duration of treatment

There was a 10-14 day run-in period (during which the subjects were to use their regular inhaled GCS), followed by a 12-week treatment period.

Criteria for evaluation (main variables)

Efficacy

- Primary endpoint was the change in mPEF from baseline (mean of the 10 last days of run-in period) to the treatment period (mean of the 12-week treatment period).
- The secondary endpoints were:
    - the change from baseline to the treatment period in evening PEF (ePEF), asthma-symptom score (day and night), night-time awakenings due to asthma symptoms, use of rescue medication (day and night), asthma-control days, and symptom-free days (main asthma-symptom variable).
    - the change in FEV_1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) from Visit 2 to the mean of Visit 3 to Visit 5.

- the change in overall score and in each domain score as measured by the standardised version of Paediatric Asthma Quality of Life Questionnaire (PAQLQ(S)) from Visit 2 to Visit 5

Safety

The safety endpoints were: cumulative incidence, severity, and type of adverse events (AEs; including changes identified by physical examination), and changes in vital signs (pulse and blood pressure), haematology, clinical chemistry, urinlysis, P-cortisol (plasma cortisol) and, in a subgroup, U-cortisol (urine cortisol) over the 12-week treatment period. No single endpoint was considered as primary.

Statistical methods

The full analysis set was used, comprising all subjects receiving active treatment, i.e. an intention-to-treat approach. All of the 622 randomised subjects who received an investigational product were evaluable for safety.

The primary variable, mPEF, was analysed using an analysis of variance (ANOVA) model with treatment and country as fixed factors, and the mean run-in value as covariate.

For the secondary objective of comparing the two Symbicort groups, a per-protocol analysis (stability analysis) was performed regarding mPEF. This analysis excluded all subjects who violated the inclusion, exclusion, or randomisation criteria.

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

Subject population

Table S1. Treatment group comparison of demography and disease-related data. For categorical data, frequencies are given; for other data, mean values and ranges are given

Variable	Symbicort pMDI	Pulmicort pMDI	Symbicort Turbuhaler	ALL
Population				
N randomised	203	207	212	622
Sex				
Male	132	137	141	410
Female	71	70	71	212
Age (yrs)	8	9	8	9
	(6-11)	(6-11)	(6-11)	(6-11)
Inhaled GCS at entry (μg)	460	475	468	468
	(375-1000)	(375-1000)	(250-1000)	(250-1000)
FEV_1 (L)	1.69	1.66	1.66	1.67
	(0.77-3.00)	(0.58-3.52)	(0.73-3.06)	(0.58-3.52)
FEV_1 (% P.N.)[1]	89.4	87.1	89.1	88.5
	(44.5-131.6)	(41.9-139.5)	(43.0-131.0)	(41.9-139.5)
PEF reversibility (%)	18.3	18.8	18.7	18.6
	(–4.3-44.4)	(–3.6-47.6)	(–5.0-49.1)	(–5.0-49.1)
Disposition				
N completed	189	193	201	583
N discontinued	14	14	11	39
N analysed for efficacy (mPEF)	203	206	212	621
N analysed for efficacy-stability analysis (mPEF)	169	184	182	535
N analysed for safety	203	207	212	622

1. Predicted normal

All but 249 subjects were Caucasians. Of the remaining subjects, 17 were Black, 47 were Oriental, and 185 were coded as Other (coded as Mixed in the database). During the last 10 days of the run-in period, 121 (19%) subjects used no rescue medication, 4 (1%) subjects had no asthma symptoms, and 325 (52%) subjects did not have any nights with awakenings due to asthma.

The treatment groups were comparable at baseline and the discontinuation rate was similar in the three treatment groups.

Efficacy results

Symbicort pMDI 80/4.5 µg 2 actuations b.i.d. was shown to be superior to Pulmicort pMDI 100 µg 2 actuations b.i.d. in increasing mPEF, the primary variable of the study. The mean value of mPEF was 9.5 L/min higher in the Symbicort pMDI group than in the Pulmicort pMDI group ($P<0.001$; Table S2).

Results for the secondary variables ePEF and FEV_1 supported that for the primary variable with statistically significant improvements in favour of Symbicort pMDI over Pulmicort pMDI. For the other secondary variables, daytime and night-time asthma-symptom scores, symptom-free days, night-time awakenings due to asthma symptoms, use of rescue medication (day and night), asthma-control days, FVC, and PAQLQ(S) scores, no statistically significant difference could be demonstrated between the two treatment groups.

Therapeutic equivalence between Symbicort pMDI and Symbicort Turbuhaler was confirmed by obtaining a mPEF value which was within the pre-specified equivalence limits of ±15 L/min (-0.7 L/min; 95% conf. limit -6.0, 4.6). Also the stability analysis of the mPEF comparison between the two Symbicort treatments confirmed therapeutic equivalence. In addition, no differences between the two Symbicort groups were shown for the other lung-function parameters, as well as for night-time awakenings, total asthma-symptom score, asthma-control day, symptom-free days, use of rescue medication, and PAQLQ(S) overall score.

Table S2. Period means, ranges, and treatment comparisons for mPEF

Treatment group	N	Run-in period		Treatment period		Adjusted[1] mean change
		mean (L/min)	(range)	mean (L/min)	(range)	
Symbicort pMDI	203	220.0	(106-386)	245.3	(98-409)	29.5
Pulmicort pMDI	206	221.3	(120-389)	236.5	(119-446)	19.9
Symbicort Turbuhaler	212	217.6	(112-379)	244.0	(147-407)	30.2

Treatment comparison	Mean difference (L/min)	95% conf. limit	P-value
Symbicort pMDI vs. Pulmicort pMDI	9.5	(4.2, 14.9)	<0.001
Symbicort pMDI vs. Symbicort Turbuhaler	-0.7	(-6.0, 4.6)	0.78
Symbicort Turbuhaler vs. Pulmicort pMDI	10.3	(5.0, 15.6)	<0.001

1. ANOVA, adjusted for country and baseline.

Safety results

The proportion of subjects reporting one or more AE was 45% in the Symbicort pMDI group, 47% in the Symbicort Turbuhaler group and 39% in the Pulmicort pMDI group. The most frequently reported AE for all three treatments was nasopharyngitis. The incidence of asthma aggravated was higher in the Pulmicort pMDI group (13 (6%)) compared with the Symbicort pMDI group (7 (3%)) and the Symbicort Turbuhaler group (7 (3%)). Most of the AEs were of mild to moderate intensity. No deaths occurred during the course of the study. Only 5 SAEs were reported in the study; 3 in the Pulmicort pMDI group and 2 in the Symbicort Turbuhaler group. The proportion of subjects who discontinued the study due to AEs was relatively low, in total 11 subjects; 3 (1%) in the Symbicort pMDI group, 7 (3%) in the Pulmicort pMDI group, and 1 (< 0.5%) in the Symbicort Turbuhaler group. No OAEs were identified in the study. At the end of treatment, there were no statistically significant differences in P-cortisol between Symbicort pMDI and Symbicort Turbuhaler. However, there was a statistically significant difference between Symbicort pMDI and Symbicort Turbuhaler regarding 24-hour U-cortisol. This difference, with the adjustment for baseline, implies higher values in the Symbicort pMDI group.