AstraZeneca

Drug product:	Symbicort pMDI	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Budesonide/formoterol		
Document No.:	SD-039-CR-0681	Referring to part of the dossier	
Edition No.:	1		
Study code:	SD-039-0681		
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A randomised, double-blind, parallel-group, multicentre phase-III study to compare the efficacy and safety of Symbicort® pMDI (budesonide/formoterol 160/4.5 μg 2 actuations b.i.d., delivered dose) with that of Pulmicort® pMDI (budesonide 200 μg 2 actuations b.i.d., metered dose) and Symbicort Turbuhaler® (budesonide/formoterol 160/4.5 μg 2 inhalations b.i.d., delivered dose) in adolescents and adults with asthma

Study centres

This study was conducted in Brazil (7 centres), Bulgaria (5 centres), Canada (9 centres), Hungary (9 centres), Mexico (7 centres), the Philippines (6 centres), Thailand (5 centres), and the UK (14 centres).

Publications

None at the time of writing this report.

Study dates:

First subject enrolled	30 April, 2002
Last subject completed	6 February, 2003

Clinical Study Report Synopsis Document No. SD-039-CR-0681 Edition No. 1 Study code SD-039-0681	(For national authority use only)

Phase of Development

Therapeutic confirmatory (III)

Objectives

The *primary objective* of the study was to show that Symbicort® pressurised metered dose inhaler (pMDI) 160/4.5 µg 2 actuations twice daily (b.i.d.) was more efficacious than Pulmicort® pMDI 200 µg 2 actuations b.i.d. over a 12-week treatment period in adolescents and adults with asthma.

The *secondary objectives* of the study were:

1. To compare the efficacy of Symbicort pMDI 160/4.5 µg 2 actuations b.i.d. with that of Symbicort Turbuhaler® 160/4.5 µg 2 inhalations b.i.d. over a 12-week treatment period in adolescents and adults with asthma.
2. To investigate the safety profile of Symbicort pMDI 160/4.5 µg 2 actuations b.i.d., Symbicort Turbuhaler 160/4.5 µg 2 inhalations b.i.d., and Pulmicort pMDI 200 µg 2 actuations b.i.d. over a 12-week treatment period in adolescents and adults with asthma.

Study design

This was a multinational and multicentre study with a randomised, double-blind, 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) and Symbicort Turbuhaler in the treatment of subjects with asthma.

Target subject population and sample size

Out-patients of either sex, age ≥12 years, with asthma not adequately controlled on inhaled glucocorticosteroids (GCSs) alone, daily using 500 - 1600 µg of inhaled GCS, and with pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% and ≤90% of predicted normal. The subjects had to have a total asthma-symptom score (night-time plus daytime) of ≥1 on at least 4 of the last 7 days of the run-in period.

About 800 subjects were to be enrolled, whereof approximately 660 needed to be randomised in order to reach 600 evaluable subjects after 12 weeks (200 in each treatment arm) for having a 90% chance of detecting a true difference in mean change in morning peak expiratory flow (mPEF) of 13 L/min between treatments. A standard deviation of 40 L/min was assumed 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 -15 L/min and 15 L/min. Assuming a standard deviation of 40 L/min, there was 90% probability for this confidence interval to be contained within the equivalence limits given that the actual difference was <1.5 L/min.

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

Symbicort pMDI (budesonide/formoterol) 160/4.5 µg (delivered dose) 2 actuations b.i.d. for inhalation (batch numbers P6041/A and P6353). The propellant used in Symbicort pMDI is the hydrofluoroalkane (HFA) 227.

Pulmicort pMDI (budesonide) 200 µg (metered dose) 2 actuations b.i.d. for inhalation (batch number P6355). The propellants used in Pulmicort pMDI are the chlorofluorocarbons (CFC) 11, 12, and 114. A 200 µg metered dose of Pulmicort corresponds to 160 µg delivered dose of the budesonide component in Symbicort.

Symbicort Turbuhaler (budesonide/formoterol) 160/4.5 µg (delivered dose) 2 inhalations twice daily (batch no. P6464).

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 randomised treatment period.

Criteria for evaluation (main variables)

Efficacy

- Primary endpoint was the change in mPEF from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 12-week treatment period).
- 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), symptom-free days (main asthma symptom variable), and asthma-control days.
  - the change in FEV_1 and forced vital capacity (FVC) 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 Asthma Quality of Life Questionnaire (AQLQ(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), changes in vital signs (pulse and blood pressure), haematology, clinical chemistry, and urinalysis 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. Of the 680 randomised subjects who received an investigational product, one subject lacked data after randomisation and therefore, 679 subjects 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 a 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.

Subject population

Table S1. Treatment group comparison of demographic and disease 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 randomized	234	217	229	680
Sex				
Male	94	68	89	251
Female	140	149	140	429
Age (yrs)	40	40	39	40
	(12-78)	(12-79)	(11-78)	(11-79)
Age Category				
12-17 (yrs)[1]	41	35	33	109
18-64 (yrs)	177	162	181	520

(Continued)

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

Variable	Symbicort pMDI	Pulmicort pMDI	Symbicort Turbuhaler	ALL
≥65 (yrs)	16	20	15	51
Inhaled GCS at entry (µg)	776	759	774	770
	(400-1600)	(400-1600)	(500-1600)	(400-1600)
FEV_1 (L)	2.07	2.01	2.09	2.06
	(0.94-4.12)	(0.85-4.25)	(1.05-3.75)	(0.85-4.25)
FEV_1 (% P.N.)[2]	71	71	69	70
	(39-92)	(45-91)	(50-90)	(39-92)
Reversibility (%)	25	25	24	25
	(12-203)	(9-104)	(12-129)	(9-203)
Disposition				
N completed	206	188	206	600
N discontinued	27	29	23	79
N analysed for efficacy (mPEF)	229	216	223	668
N analysed for efficacy- stability analysis (mPEF)	209	204	207	620
N analysed for safety	233	217	229	679

1. Including one subject 11 years and 354 days old at Visit 1 in the Symbicort Turbuhaler group.
2. P.N.=Predicted normal

All but 240 subjects were Caucasians (10 were Black, 140 were Oriental, and 90 were coded as Other). During the last 10 days of run-in, 61 (9%) subjects used no rescue medication, 2 (0%) subjects had no asthma symptoms and 251 (38%) subjects did not have any nights with awakenings due to asthma.

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

Efficacy results

Symbicort pMDI 160/4.5 µg 2 actuations b.i.d. was shown to be superior to Pulmicort pMDI 200 µg 2 actuations b.i.d. in increasing mPEF, the primary variable of the study. The mean value of mPEF was 29 L/min higher in the Symbicort pMDI group than in the Pulmicort pMDI group (P<0.001; Table S2).

The results for secondary variables supported that for the primary variable with statistically significant improvements in favour of Symbicort pMDI over Pulmicort

pMDI for ePEF, 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, FEV_1, FVC, and AQLQ(S) scores.

Therapeutic equivalence between Symbicort pMDI and Symbicort Turbuhaler was confirmed by obtaining a 95% confidence interval for the difference in mPEF, which was within the pre-specified equivalence limits of ±15 L/min (-3 L/min; 95% conf. limits -10.4, 4.9). Also the stability analysis of the mPEF comparison between the two Symbicort treatments confirmed the therapeutic equivalence. In addition, no differences between the two Symbicort groups could be demonstrated for the other lung function parameters as well as for night-time awakenings, total asthma-symptom score, use of rescue medication, and AQLQ(S) overall score. Symbicort Turbuhaler was slightly more effective than Symbicort pMDI in decreasing daytime asthma-symptom score and in increasing the number of symptom-free days and asthma-control days.

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	229	326.3	(89 - 715)	355.6	(100 - 801)	29.3
Pulmicort pMDI	216	317.6	(109 - 638)	318.7	(108 - 656)	0.6
Symbicort Turbuhaler	223	320.6	(93 - 668)	352.9	(91 - 686)	32.0
Treatment comparison		Mean diff. (L/min)		95% conf. limits		P-value
Symbicort pMDI vs. Pulmicort pMDI		28.6		(20.9, 36.4)		<0.001
Symbicort pMDI vs. Symbicort Turbuhaler		-2.8		(-10.4, 4.9)		0.48
Symbicort Turbuhaler vs. Pulmicort pMDI		31.4		(23.7, 39.2)		<0.001

1. ANOVA, adjusted for country and baseline.

Safety results

The proportion of subjects reporting AEs was relatively low with 32% of the subjects reporting one or more AEs. The most frequently reported AE, for all three treatment groups, was nasopharyngitis. The AEs were mostly of mild to moderate intensity. No deaths occurred during the course of the study. Four subjects experienced Serious Adverse Events (SAEs), whereof one SAE (increase in liver enzyme activity) was judged by the investigator to be related to pMDI. Thirty subjects, 11 in the Symbicort pMDI, 15 in the Pulmicort pMDI, and 4 in the Symbicort Turbuhaler group, discontinued the study prematurely due to AEs. The most frequently reported reason for treatment discontinuation due to AE was aggravation of

asthma; 1 subject in the Symbicort pMDI group, 7 subjects in the Pulmicort pMDI group, and 2 subjects in the Symbicort Turbuhaler group. Overall, AEs associated with asthma (i.e. asthma aggravated, wheezing, and coughing) appeared to be less commonly reported in the Symbicort pMDI and Turbuhaler groups, when compared with the Pulmicort pMDI group.