AstraZeneca

Drug product:	Symbicort	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	budesonide/formoterol		
Document No.:	SD-039-CR-0688	Referring to part of the dossier	
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Efficacy and safety of Symbicort® (budesonide/formoterol 80/4.5 μg, 2 inhal. b.i.d.) compared to Pulmicort® (budesonide 100 μg, 2 inhal. b.i.d.) and Pulmicort (budesonide 100 μg, 2 inhal. b.i.d.) plus Oxis® (formoterol 4.5 μg, 2 inhal. b.i.d.) all delivered via Turbuhaler® in steroid using asthmatic children. A double-blind, double-dummy, randomised, parallel-group, phase III, multicentre 12-week study.

Study centres

The study was conducted in eight countries and included 80 centres that enrolled patients; Austria (5), Belgium (11), Czech Republic (14), France (11), Hungary (12), Poland (17), Spain (8) and Switzerland (2).

Publications

None at the time of writing this report.

Study dates:

First subject enrolled 11 March, 2002

Last subject completed 10 March, 2003

Phase of Development

Therapeutic confirmatory (III)

Objectives

The *primary objective* of the study was to show that the efficacy of Symbicort® Turbuhaler® 80/4.5 µg, 2 inhalations morning and evening is superior to that of Pulmicort® Turbuhaler 100 µg, 2 inhalations morning and evening, over a 12-week treatment period in children with asthma.

The *secondary objectives* were:

1. To compare the efficacy of Symbicort Turbuhaler 80/4.5 µg, 2 inhalations morning and evening with that of Pulmicort Turbuhaler 100 µg, 2 inhalations morning and evening plus Oxis Turbuhaler 4.5 µg, 2 inhalations morning and evening over a 12-week treatment period in children with asthma.
2. To investigate the safety profile of Symbicort Turbuhaler 80/4.5 µg, 2 inhalations morning and evening, Pulmicort Turbuhaler 100 µg, 2 inhalations morning and evening and Pulmicort Turbuhaler 100 µg, 2 inhalations morning and evening plus Oxis Turbuhaler 4.5 µg, 2 inhalations morning and evening over a 12-week treatment period in children with asthma.

Study design

This was a randomised, double-blind, double-dummy, parallel-group, active-controlled, multicentre, 12-week study with a 2-week run-in period, comparing the efficacy and safety of Symbicort with that of Pulmicort and Pulmicort plus Oxis in asthmatic children using inhaled glucocorticosteroids (GCS).

Target patient population and sample size

Male or female patients aged 4-11 years with asthma treated with 375-1000 µg/day of inhaled GCS. They should have a history of exercise-induced bronchoconstriction on average at least once a week. The patients should have been symptomatic by showing asthma symptoms on at least 4 of the last 7 days of the run-in period. Moreover they should have had a mean morning PEF during the 7 last days of the run-in period of 50–85% of the postbronchodilatory PEF obtained at Visit 1. In order to have 540 evaluable patients (180 patients in each treatment arm), 600 patients were needed to be randomised.

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

Symbicort Turbuhaler (budesonide/formoterol), 80/4.5 µg, 2 inhalations morning and evening. Pulmicort Turbuhaler (budesonide), 100 µg, 2 inhalations morning and evening alone or together with Oxis Turbuhaler (formoterol), 4.5 µg, 2 inhalations morning and evening. For information about placebo and batch numbers, see Table 3.

Duration of treatment

There was a 10-14-day run-in period (during which the patients were using their regular inhaled GCS). After the run-in period the patients entered a 12-week treatment period.

Criteria for evaluation (main variables)

Efficacy

- The primary variable was the change from baseline (average of the last 10 days of the run-in period) to treatment (average of the 12-week treatment period) in morning PEF.
- The secondary variables were:

  -the change from baseline (average of the last 10 days of the run-in period) to treatment (average of the 12-week treatment period) in evening PEF, asthma symptom score (day and night), night-time awakenings due to asthma symptoms, symptom-free days, use of rescue medication (day and night), rescue-free days and asthma-control days.

  -the change from baseline (Visit 2) to the average of all treatment period measurements (Visit 3 to Visit 5) for FEV_1 and FVC.

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

Safety

Safety was assessed by the incidence, severity and type of AEs (including findings identified at the physical examination), and changes in vital signs (pulse and blood pressure), p-cortisol and, in a subpopulation, 24-hour u-cortisol over the 12-week treatment period. No single endpoint was considered as primary.

Statistical methods

The statistical analysis was based on the full analysis set. Additional analyses were performed to check the stability of the results.

The primary objective, to show that Symbicort Turbuhaler is more effective than Pulmicort Turbuhaler, was achieved using a t-test under the assumed analysis of variance (ANOVA) model.

All hypothesis testings were done with two-sided alternative hypothesis and p-values less than 5% were considered statistically significant.

Patient population

Table S1. Patient population and disposition

		Symbicort	Pulmicort	Pulmicort+Oxis	ALL
Population					
N enrolled					809
N randomised (planned)		216 (200)	213 (200)	201 (200)	630 (600)
Demographic characteristics					
Sex (n and % of patients)	Male	140 (65)	147 (69)	137 (68)	424 (67)
	Female	76 (35)	66 (31)	64 (32)	206 (33)
Age (years)	Mean (range)	8.1 (4–11)	8.2 (4–11)	8.1 (4-11)	8.1 (4-11)
Race (n and %)	Caucasian	214 (99)	211 (99)	200 (100)	625 (99)
	Other	2 (1)	2 (1)	1 (0)	5 (1)
Inhaled GCS dose (μg) at entry	Mean (range)	464.5 (320–1000)	446.2 (200–1000)	450.0 (200–1000)	453.7 (200–1000)
Baseline characteristics					
FEV_1 (L)	Mean (range)	1.64 (0.7–3.0)	1.65 (0.6–3.4)	1.66 (0.6–3.3)	1.65 (0.6–3.4)
FEV_1 (% P.N.)	Mean (range)	91.9 (50–166)	91.3 (52–132)	93.0 (45–169)	92.0 (45–169)
Symptom-free days (%)	Mean (range)	19.4 (0–90)	20.8 (0–100)	17.6 (0–80)	19.3 (0–100)
Mean total symptom score (0–6)	Mean (range)	1.52 (0.1–3.9)	1.37 (0.0–4.9)	1.46 (0.3–5.0)	1.45 (0–5)
Disposition					
N (%) of patients who	completed	202 (94)	200 (94)	190 (95)	592 (94)
	discontinued	14 (6)	13 (6)	11 (5)	38 (6)
N analysed for safety		216	213	201	630
N analysed for efficacy		216	213	201	630

The different groups were balanced in baseline characteristics.

The most common reason for discontinuation in each group was that the eligibility criteria was not fulfilled.

Efficacy results

Table S2. Treatment comparisons for diary card variables

Variable	Treatment	Mean difference	95% conf.limits	P-value
PEF (L/min)				
-morning	Symbicort vs. Pulmicort	10.9	(5.4, 16.4)	<0.001
	Symbicort vs. Pulmicort+Oxis	-4.2	(-9.8, 1.3)	0.14
	Pulmicort+Oxis vs. Pulmicort	15.1	(9.5, 20.7)	<0.001
-evening	Symbicort vs. Pulmicort	9.1	(3.8, 14.5)	<0.001
	Symbicort vs. Pulmicort+Oxis	-3.2	(-8.6, 2.3)	0.25
	Pulmicort+Oxis vs. Pulmicort	12.3	(6.9, 17.8)	<0.001
Asthma symptoms				
-total daily score (0-6)	Symbicort vs. Pulmicort	-0.04	(-0.15, 0.08)	0.53
	Symbicort vs. Pulmicort+Oxis	-0.05	(-0.17, 0.07)	0.40
	Pulmicort+Oxis vs. Pulmicort	0.01	(-0.11, 0.13)	0.83
-night-time score (0-3)	Symbicort vs. Pulmicort	-0.02	(-0.07, 0.04)	0.58
	Symbicort vs. Pulmicort+Oxis	-0.03	(-0.09, 0.02)	0.25
	Pulmicort+Oxis vs. Pulmicort	0.02	(-0.04, 0.08)	0.55
-daytime score (0-3)	Symbicort vs. Pulmicort	-0.01	(-0.08, 0.06)	0.76
	Symbicort vs. Pulmicort+Oxis	-0.01	(-0.08, 0.06)	0.71
	Pulmicort+Oxis vs. Pulmicort	0.00	(-0.07, 0.07)	0.95
-awakenings (%)	Symbicort vs. Pulmicort	-0.2	(-2.4, 2.0)	0.87
	Symbicort vs. Pulmicort+Oxis	-0.8	(-3.0, 1.5)	0.50
	Pulmicort+Oxis vs. Pulmicort	0.6	(-1.7, 2.8)	0.61
-symptom-free days (%)	Symbicort vs. Pulmicort	0.9	(-4.6, 6.4)	0.74
	Symbicort vs. Pulmicort+Oxis	0.4	(-5.2, 6.0)	0.89
	Pulmicort+Oxis vs. Pulmicort	0.5	(-5.1, 6.2)	0.86
Use of rescue medication				
-total daily No. of inhalations	Symbicort vs. Pulmicort	-0.04	(-0.14, 0.06)	0.47
	Symbicort vs. Pulmicort+Oxis	-0.06	(-0.16, 0.04)	0.25
	Pulmicort+Oxis vs. Pulmicort	0.02	(-0.08, 0.13)	0.66
-night-time	Symbicort vs. Pulmicort	-0.01	(-0.04, 0.02)	0.59
	Symbicort vs. Pulmicort+Oxis	-0.02	(-0.05, 0.02)	0.30
	Pulmicort+Oxis vs. Pulmicort	0.01	(-0.02, 0.04)	0.61
-daytime	Symbicort vs. Pulmicort	-0.03	(-0.11, 0.05)	0.44

(Continued)

Table S2. Treatment comparisons for diary card variables

Variable	Treatment	Mean difference	95% conf.limits	P-value
	Symbicort vs. Pulmicort+Oxis	-0.04	(-0.13, 0.04)	0.28
	Pulmicort+Oxis vs. Pulmicort	0.01	(-0.07, 0.10)	0.74
-rescue-free days (%)	Symbicort vs. Pulmicort	2.2	(-1.7, 6.2)	0.27
	Symbicort vs. Pulmicort+Oxis	3.2	(-0.8, 7.3)	0.12
	Pulmicort+Oxis vs. Pulmicort	-1.0	(-5.1, 3.1)	0.63
Asthma-control days				
-% of days	Symbicort vs. Pulmicort	0.9	(-4.7, 6.5)	0.75
	Symbicort vs. Pulmicort+Oxis	0.9	(-4.8, 6.6)	0.75
	Pulmicort+Oxis vs. Pulmicort	-0.0	(-5.7, 5.7)	1.0

Table S3. Treatment comparisons for spirometry variables.

Variable	Treatment	Mean diff.	95% conf.limits	P-value
FEV_1 (L)	Symbicort vs. Pulmicort	0.078	(0.041, 0.114)	<0.001
	Symbicort vs. Pulmicort+Oxis	0.019	(-0.017, 0.056)	0.30
	Pulmicort+Oxis vs. Pulmicort	0.058	(0.021, 0.095)	0.0020
FVC (L)	Symbicort vs. Pulmicort	0.024	(-0.014, 0.061)	0.22
	Symbicort vs. Pulmicort+Oxis	0.011	(-0.027, 0.049)	0.58
	Pulmicort+Oxis vs. Pulmicort	0.013	(-0.026, 0.051)	0.51

Symbicort 80/4.5 µg, 2 inhalations twice daily, statistically significantly improved lung function compared with the corresponding dose of Pulmicort (11 L/min for mPEF, 9 L/min for ePEF and 0.08 L for FEV_1), but there was no evidence of a difference in effect on lung function between Symbicort and the combination of Pulmicort and Oxis at corresponding doses. Symbicort did not give any benefit over Pulmicort regarding effect on symptoms or PAQLQ(S) in this population.

Safety results

Only 39% of the patients in this study reported an AE. The overall incidence, both on a SOC level and on a preferred term level, was similar between the treatment groups. Respiratory infection and rhinitis were the most frequently reported AEs. The incidence of well-known class-effects of inhaled GCS and β_2-agonists were very low and similar between the treatments. No clinically important differences between the treatment groups

were observed with regard to the nature and incidence of AEs including SAEs and DAEs. Regarding vital signs and laboratory measurements (morning p-cortisol and 24-hour u-cortisol) no apparent differences between the treatments were observed.
The three treatments were well tolerated and no new safety findings were identified.