AstraZeneca

Drug Product	Symbicort Turbuhaler	**Synopsis**	(For national authority use only)
Drug substance(s)	Budesonide/formoterol		
Document No.	SD-039-CR-0689	Referring to part of the dossier	
Edition No.	1		
Study Code	SD-039-0689		
Date	18 Dec, 2002		

Efficacy and safety of Symbicort® (budesonide/formoterol) 1280/36 μg daily delivered dose compared to Pulmicort® (budesonide) 1600 μg metered dose and Pulmicort (budesonide) 1600 μg metered dose plus Oxis® (formoterol) 36 μg delivered dose all delivered via Turbuhaler® in steroid-using asthmatic adolescents and adults. A double-blind, double-dummy, randomized, parallel group, phase III, multicentre study.

Study centres

This study was conducted in Australia (11 centres), Austria (6 centres), Czech Republic (15 centres), France (9 centres), Poland (8 centres), and Spain (5 centres).

Publications

None at the time of writing this report.

Study dates

Study Dates	First subject entered: 9 July, 2001 Last subject completed: 14 June, 2002
Phase of development	IIIb

Synopsis Document No. SD-039-CR-0689 Study Code SD-039-0689	(For national authority use only)

Objectives

The primary objective was to compare the efficacy of Symbicort (budesonide/formoterol) with that of Pulmicort (budesonide) in steroid-using asthmatic adolescent and adult subjects during 12 weeks of treatment.

The primary comparison was between Symbicort and Pulmicort. A secondary comparison was between Symbicort and Pulmicort + Oxis (formoterol).

The primary efficacy variable was morning Peak Expiratory Flow (PEF) as registered daily in diary cards. Secondary efficacy variables included the following diary card variables: evening PEF, inhalations of the rescue medication (day and night), nights with awakenings due to asthma symptoms, asthma symptom scores (day and night), asthma control days, and mild exacerbation days. FEV_1, FVC, and Work Productivity and Activity Impairment (WPAI) were other secondary variables. Two additional variables were added after clean file: symptom free days and rescue free days.

A secondary objective was to study safety during 24 weeks of treatment by the evaluation of adverse events (AEs), ECG, s-glucose, s-potassium, physical examination, pulse, blood pressure, morning p-cortisol and stimulated p-cortisol (ACTH-test).

Study design

The study is a 24-week, double-blind, double-dummy, randomized, reference-controlled, parallel-group, multicentre study comparing the efficacy and safety of Symbicort (budesonide/formoterol) at a daily dose of 1280/36 µg delivered dose compared to Pulmicort (budesonide) 1600 µg metered dose and Pulmicort 1600 µg metered dose plus Oxis (formoterol) 36 µg delivered dose in adolescent and adult subjects with asthma.

The subjects in the Symbicort and Pulmicort + Oxis group received their treatment for 24 weeks. The subjects in the Pulmicort group were switched after 12 weeks of treatment to either Symbicort or Pulmicort + Oxis for an additional 12 weeks of treatment.

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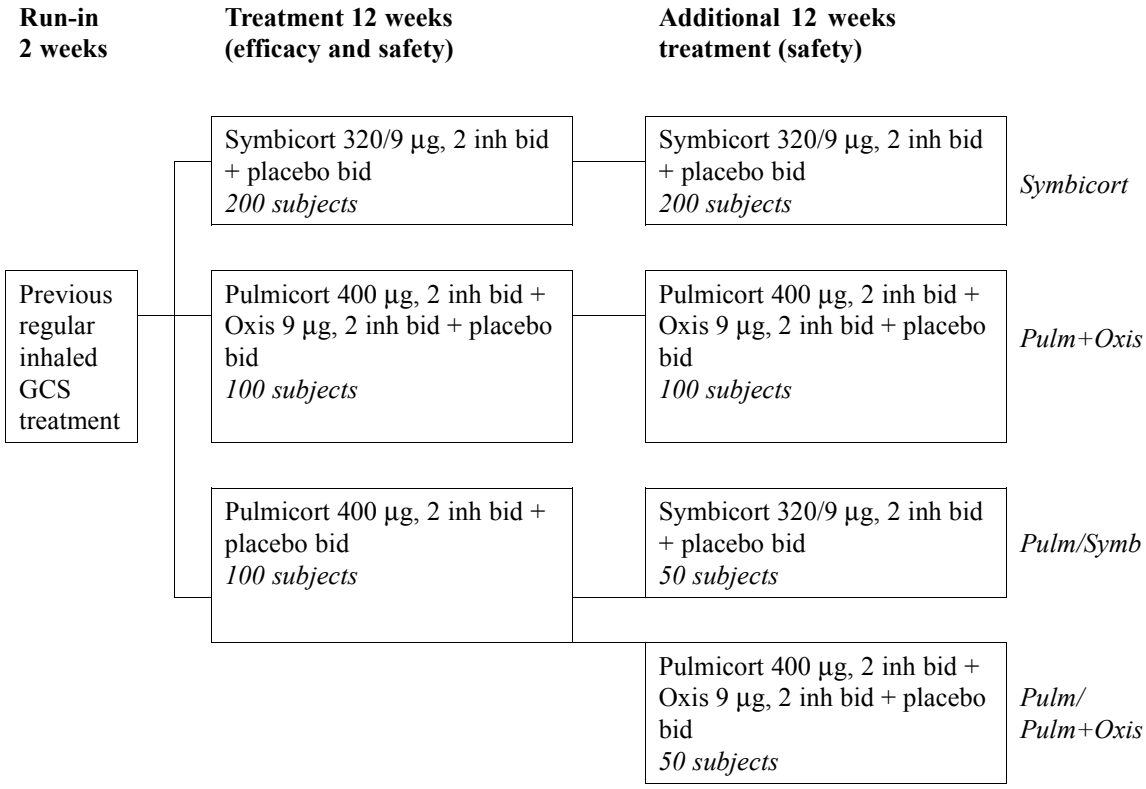

Target subject population and sample size

Male and female subjects, ages 12 and above, with asthma currently treated with ≥ 750 µg per day of inhaled glucocorticosteroid (GCS), with reversible airway obstruction (defined as postbronchodilator increase in FEV_1 of ≥ 15% relative to baseline for all subjects and ≥ 200 mL for subjects ≥ 18 years), and with a pre-bronchodilator FEV_1 ≥ 40% and ≤ 85% of predicted at Visit 1 were enrolled. At Visit 2, the total daily asthma symptom score, on a scale of 0-6, was to be ≥ 1 on at least 4 of the last 7 days of the run-in period. A two group t-test with a 5% two-sided significance level would have 90% power to detect a difference in change in morning PEF of 18 L/min when the sample sizes in these two groups (Pulmicort and Symbicort) were 100 and 200, respectively, assuming that the common standard deviation was 45 L/min.

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

Symbicort® (budesonide/formoterol) Turbuhaler® 320/9 µg per inhalation, 2 inhalations twice daily, batch numbers: CA11, CA12.
Placebo to match Symbicort, batch numbers: CC20, BL19.

Pulmicort® (budesonide) Turbuhaler® 400 µg per inhalation, 2 inhalations twice daily, batch number: CD724.
Placebo to match Pulmicort, batch number: CD29.
Oxis® (formoterol) Turbuhaler® 9 µg per inhalation, 2 inhalations twice daily, batch number: CC798.
Placebo to match Oxis, batch numbers: CI40, CD39, CB38.
Rescue medication: Bricanyl® (terbutaline) Turbuhaler® 0.5 mg per inhalation, batch numbers: CB1177, BC1161, BH1170.
Synacthen test: Synacthen batch number: S07200, S07400

Duration of treatment

The run-in period, during which the subjects were treated with their regular inhaled GCS, was 2 weeks, and the randomized treatment was 24 weeks, 12 weeks with three treatment arms (Symbicort, Pulmicort, and Pulmicort + Oxis) plus 12 weeks with two treatments (Symbicort and Pulmicort + Oxis).

Criteria for evaluation (main variables)

Efficacy

- Primary variable: morning PEF
- Secondary variables: evening PEF, inhalations of the rescue medication (day and night), nights with awakenings due to asthma symptoms, asthma symptom scores (day and night), asthma control days, mild exacerbation days, FEV_1, FVC, and WPAI. Symptom free days and rescue free days were added after clean file.

Safety

Safety was evaluated through the collective evaluation of the following: Adverse events (AEs), ECG, s-glucose, s-potassium, physical examination, pulse, blood pressure, morning p-cortisol, and ACTH-stimulated p-cortisol.

Statistical methods

An intention to treat (ITT) analysis was used. The primary endpoint was the change in morning PEF from baseline to twelve weeks. For diary variables, baseline was the mean of the available data during the last 10 days of run-in and the treatment value was the mean of the available data during the first 12 weeks of treatment. For FEV_1, baseline was the value measured at Visit 2, and treatment was the mean value of available data from Visit 3 to Visit 5. The change from baseline to the treatment period in the primary

variable, morning PEF, was analysed using an analysis of variance (ANOVA) model with treatment and country as fixed factors and the baseline value as a covariate.

Subject population

Table S1. Subject population and disposition. For categorical data, frequencies are given; for other data, mean values and ranges.

Variable	Symbicort	Pulm+Oxis	Pulm/ Pulm+Oxis[1]	Pulm/Symb[1]	ALL
N	226	115	61	54	456
Demographic characteristics					
Sex					
Male	82	46	23	26	177
Female	144	69	38	28	279
Age (yrs)	46	47	45	48	46
	(13-79)	(12-79)	(13-73)	(16-74)	(12-79)
BMI (kg/m^2)	27	27	26	26	27
	(13-46)	(16-44)	(19-45)	(17-39)	(13-46)
Time since diagnosis (yrs) [2]	8	10	9	6	8
	(1-56)	(1-66)	(1-54)	(1-61)	(1-66)
IGCS at entry (μg)	1033	1036	1047	1057	1038
	(250-2000)	(500-4000)	(750-3200)	(800-2000)	(250-4000)
Baseline characteristics					
FEV_1 (L)	2.07	1.97	2.00	2.03	2.03
	(0.74-3.92)	(0.63-3.88)	(0.80-3.60)	(1.05-3.73)	(0.63-3.92)
FEV_1 (% P.N.)	67	65	65	66	66
	(36-88)	(40-85)	(41-85)	(41-85)	(36-88)
Rescue free days (%)	30	28	24	27	28
	(0-100)	(0-100)	(0-100)	(0-100)	(0-100)
Mean symptom score	1.8	1.8	1.9	1.7	1.8
	(0.3-6.0)	(0.4-3.9)	(0.3-4.1)	(0.3-3.6)	(0.3-6.0)
Symptom free days (%)	12	10	7	10	11
	(0-70)	(0-70)	(0-89)	(0-60)	(0-89)
Asthma control days (%)	10	9	5	8	9
	(0-70)	(0-70)	(0-56)	(0-60)	(0-70)

(Continued)

Table S1. Subject population and disposition. For categorical data, frequencies are given; for other data, mean values and ranges.

Variable	Symbicort	Pulm+Oxis	Pulm/ Pulm+Oxis[1]	Pulm/Symb[1]	ALL
Disposition					
Subjects who completed	196	104	52	48	400
Subjects who discontinued	30	11	9	6	56
Analysed for efficacy	226	115	61	54	456
Analysed for safety	226	115	61	54	456

1. Subjects in the Pulmicort group were switched to Pulmicort + Oxis or Symbicort after the first 12 weeks of treatment
2. Median

The groups were comparable for demographic characteristics and had similar baseline lung function.

Efficacy results

Symbicort 320/9 µg 2 inhalations twice daily (1280/36 µg total daily delivered dose) was more effective than Pulmicort 400 µg 2 inhalations twice daily (1600 µg total daily metered dose) in increasing morning PEF, the primary variable of the study, over 12 weeks of treatment in asthmatic subjects not well controlled on inhaled GCS. The mean difference was 32.9 L/min ($p<0.001$). Similar improvements were observed in the Pulmicort + Oxis group as in the Symbicort group. The 95% confidence interval for the difference between Symbicort and the free combination (Pulmicort + Oxis) was entirely within the generally accepted equivalence limits for PEF (± 15 L/min). Results for secondary variables supported those for the primary variable with statistically significant improvements in favour of Symbicort over Pulmicort for evening PEF, total asthma symptom score, daytime asthma symptoms, symptom free days, use of rescue medication/ 24 hours, rescue free days, asthma control days, time to first mild exacerbation, and FEV_1. There was no statistically significant difference between Symbicort and Pulmicort + Oxis for any variable. In Table S2, a summary of the results is shown.

Table S2. Treatment comparisons for efficacy variables.

Variable	Treatment	Mean[1] difference	95% Conf.Limits	P-value
PEF (L/min)				
-morning	Symbicort vs. Pulmicort	32.9	(23.5, 42.3)	<0.001
	Pulm+Oxis vs. Pulmicort	31.6	(20.9, 42.4)	<0.001
	Symbicort vs. Pulm+Oxis	1.3	(-8.2, 10.7)	0.79
-evening	Symbicort vs. Pulmicort	30.9	(22.1, 39.7)	<0.001
	Pulm+Oxis vs. Pulmicort	31.5	(21.3, 41.6)	<0.001
	Symbicort vs. Pulm+Oxis	-0.6	(-9.5, 8.2)	0.89
Asthma symptoms				
-total score (0-6)	Symbicort vs. Pulmicort	-0.26	(-0.44, -0.08)	0.0051
	Pulm+Oxis vs. Pulmicort	-0.30	(-0.51, -0.09)	0.0044
	Symbicort vs. Pulm+Oxis	0.04	(-0.14, 0.22)	0.63
-night-time score (0-3)	Symbicort vs. Pulmicort	-0.05	(-0.14, 0.05)	0.33
	Pulm+Oxis vs. Pulmicort	-0.05	(-0.15, 0.06)	0.36
	Symbicort vs. Pulm+Oxis	0.00	(-0.09, 0.10)	0.94
-daytime score (0-3)	Symbicort vs. Pulmicort	-0.21	(-0.31, -0.11)	<0.001
	Pulm+Oxis vs. Pulmicort	-0.25	(-0.37, -0.13)	<0.001
	Symbicort vs. Pulm+Oxis	0.04	(-0.06, 0.14)	0.45
-awakenings (%)	Symbicort vs. Pulmicort	-2.6	(-7.2, 2.0)	0.27
	Pulm+Oxis vs. Pulmicort	-1.3	(-6.7, 4.0)	0.62
	Symbicort vs. Pulm+Oxis	-1.3	(-5.9, 3.4)	0.60
-symptom free days (%)	Symbicort vs. Pulmicort	15.6	(8.4, 22.8)	<0.001
	Pulm+Oxis vs. Pulmicort	16.6	(8.4, 24.9)	<0.001
	Symbicort vs. Pulm+Oxis	-1.0	(-8.2, 6.2)	0.78
Use of rescue medication				
-total no. of inhalations/ 24 hours	Symbicort vs. Pulmicort	-0.58	(-0.86, -0.30)	<0.001
	Pulm+Oxis vs. Pulmicort	-0.70	(-1.03, -0.37)	<0.001
	Symbicort vs. Pulm+Oxis	0.12	(-0.17, 0.40)	0.41
-night-time inhalations	Symbicort vs. Pulmicort	-0.05	(-0.15, 0.06)	0.39
	Pulm+Oxis vs. Pulmicort	-0.08	(-0.20, 0.04)	0.18
	Symbicort vs. Pulm+Oxis	0.04	(-0.07, 0.14)	0.49
-daytime inhalations	Symbicort vs. Pulmicort	-0.53	(-0.74, -0.32)	<0.001
	Pulm+Oxis vs. Pulmicort	-0.61	(-0.85, -0.37)	<0.001
	Symbicort vs. Pulm+Oxis	0.08	(-0.13, 0.29)	0.44
-rescue free days (%)	Symbicort vs. Pulmicort	18.9	(11.8, 26.0)	<0.001
	Pulm+Oxis vs. Pulmicort	21.4	(13.2, 29.6)	<0.001
	Symbicort vs. Pulm+Oxis	-2.5	(-9.6, 4.7)	0.50

(Continued)

Table S2. Treatment comparisons for efficacy variables.

Variable	Treatment	Mean[1] difference	95% Conf.Limits	P-value
Asthma control days				
-% of days	Symbicort vs. Pulmicort	16.1	(8.8, 23.4)	<0.001
	Pulm+Oxis vs. Pulmicort	15.8	(7.4, 24.2)	<0.001
	Symbicort vs. Pulm+Oxis	0.3	(-7.0, 7.6)	0.94
Mild exacerbation days				
-% of days	Symbicort vs. Pulmicort	-3.6	(-8.7, 1.4)	0.16
	Pulm+Oxis vs. Pulmicort	-0.7	(-6.5, 5.1)	0.81
	Symbicort vs. Pulm+Oxis	-2.9	(-8.0, 2.2)	0.26
Mild exacerbations				
- time to first	Symbicort vs. Pulmicort	0.641	(0.475, 0.864)	0.0032
	Pulm+Oxis vs. Pulmicort	0.769	(0.546, 1.084)	0.098
	Symbicort vs. Pulm+Oxis	0.833	(0.605, 1.147)	0.13
FEV_1	Symbicort vs. Pulmicort	0.160	(0.068, 0.253)	<0.001
	Pulm+Oxis vs. Pulmicort	0.137	(0.032, 0.243)	0.011
	Symbicort vs. Pulm+Oxis	0.023	(-0.068, 0.114)	0.62
FVC	Symbicort vs. Pulmicort	0.096	(-0.009, 0.201)	0.073
	Pulm+Oxis vs. Pulmicort	0.113	(-0.007, 0.233)	0.064
	Symbicort vs Pulm+Oxis	-0.017	(-0.121, 0.086)	0.75

[1] For mild exacerbations, hazard ratio is given.

Safety results

The main focus of the safety evaluation will be the two groups for which treatment was unchanged during the 24-week study: the Symbicort and the Pulmicort + Oxis groups. The proportion of subjects reporting AEs was similar in the two treatment groups, Symbicort (51%) and Pulm+Oxis (55%). The AEs were mostly (>95%) of mild or moderate intensity. The most frequently reported AE in all treatment groups was Respiratory infection. One subject died from Pulmonary embolism after 17 weeks and two days of treatment with Symbicort; the death was not considered causally related to the investigational product. The proportion of subjects reporting SAEs, other than death, was similar in the Symbicort and Pulm+Oxis treatment groups (3% for both). No SAE

was considered by the investigator to be causally related to investigational product. The proportion of subjects reporting DAEs was 4% in the Symbicort treatment group and 5% in the Pulm+Oxis treatment group. No OAEs were identified in the study.

No clinically important differences with regards to s-potassium, s-glucose, vital signs, or ECG variables were identified between the Symbicort and the Pulm+Oxis treatment groups or within these groups over time. There were no statistically significant differences between the Symbicort and the Pulmicort + Oxis treatment groups regarding morning plasma cortisol or stimulated cortisol. Although mean plasma cortisol decreased slightly over time in all groups, 93% of the subjects in the Symbicort group and 89% of the subjects in the Pulmicort + Oxis group still had a normal response to ACTH stimulation at the end of the study.