AstraZeneca

Drug Product	Symbicort	**Synopsis**	(For national authority use only)
Drug substance(s)	Budesonide/formoterol		
Document No.	SD-039-CR-0668	Referring to part of the dossier	
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Efficacy and safety of Symbicort® (budesonide/formoterol) Turbuhaler® as Single Therapy in subjects with moderate-severe asthma. Comparison with conventional asthma therapy, Pulmicort® (budesonide) Turbuhaler® as regular treatment complemented with Bricanyl® (terbutaline) Turbuhaler®.

Study centre(s)

This was a multicentre study with 211 centres participating from the following 18 countries: Argentina (6 centres), Australia (10 centres), Canada (22 centres), Czech republic (5 centres), Finland (6 centres), France (29 centres), Germany (20 centres), Hungary (7 centres), Israel (17 centres), Italy (11 centres), Mexico (5 centres), the Netherlands (24 centres), New Zealand (4 centres), Norway (13 centres), Portugal (7 centres), Russia (6 centres), South Africa (11 centres) and Turkey (8 centres).

Publications

None at the time of finalisation of this report.

Study Dates

First subject entered: 23 May, 2001
Last subject completed: 22 January, 2003

Phase of Development

Therapeutic confirmatory (III)

Objectives

The primary objective of the study is to compare the regular use of Symbicort Turbuhaler 2 x 160/4.5 µg once daily, complemented with Symbicort Turbuhaler 160/4.5 µg as needed, with Pulmicort Turbuhaler 2 x 160 µg twice daily (bid), complemented with Bricanyl Turbuhaler 0.4 mg as-needed. The primary efficacy variable is severe asthma exacerbations.

The secondary objective of the study was to investigate safety of Symbicort Turbuhaler 2 x 160/4.5 µg once daily, complemented with Symbicort Turbuhaler 160/4.5 µg as needed, versus Pulmicort Turbuhaler 2 x 160 µg bid, complemented with Bricanyl Turbuhaler 0.4 mg as-needed . The evaluation of safety took into account several safety variables with no particular variable being chosen as the main safety variable.

Study design

This was a double-blind, double-dummy, randomized, active-controlled, parallel-group, multicentre study comparing the efficacy and safety of Symbicort 160/4.5 µg/inhalation, two inhalations once daily + Symbicort 160/4.5 µg/inhalation as-needed (Symbicort single-inhaler therapy (SiT)) with Pulmicort 160 µg/inhalation, two inhalations bid + Bricanyl 0.4 mg/inhalation as-needed, in adults and adolescents (12-80 years) for a period of 12 months in the treatment of asthma.

Target subject population and sample size

Male and female subjects, 12 to 80 years with asthma, previously treated with inhaled glucocorticosteroids (IGCS) 400-1600 µg per day, with a forced expiratory volume in one second (FEV_1) of 50-90% of predicted normal (% P.N.), a history of at least one clinical important asthma exacerbation 1-12 months prior to inclusion, a reversibility in FEV_1 from baseline of at least 12%, and who had an asthma symptom score ≥ 1 during 4 of the last 7 days of the run-in period.

If the true incidence of severe asthma exacerbations in one of the groups is 25%, a sample size of 800 randomised subjects per group gives 80% probability of detecting a reduction of the incidence to 19.2 % in the other group. This assumes a confidence level of 5% and a two-sided alternative hypothesis in the log-rank test for equality of survival curves.

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

Symbicort (budesonide/formoterol fumarate dihydrate) Turbuhaler 160/4.5 µg/inhalation, two inhalation once daily + Symbicort 160/4.5 µg/inhalation as-needed or Pulmicort

(budesonide) 160 µg/inhalation, two inhalations bid + Bricanyl (terbutaline sulphate) Turbuhaler® 0.4 mg/inhalation as-needed. Doses were given in three different inhalers, identical between treatments, i.e. one inhaler for morning regular treatment (Placebo or Pulmicort), one inhaler for evening regular treatment (Symbicort or Pulmicort) and one inhaler for as-needed use (Symbicort or Bricanyl). Batch numbers were: Symbicort Turbuhaler; BI 25, CD 27, CM 28. Pulmicort turbuhaler; CD 13, CI 14. Bricanyl Turbuhaler; BG 24, BL 26, CC 27, CC 28, CC 29, CC 30, CI 32. Placebo turbuhaler; BL 11, CD 12.

N.B. Treatment with Symbicort, both regularly and as-needed, will be referred to as Symbicort SiT, and treatment with Pulmicort regularly and Bricanyl as-needed will be referred to as Pulmicort.

Duration of treatment

A 12-month treatment period preceded by a 2-week run-in period.

Criteria for evaluation (main variables)

Efficacy

- Primary efficacy variable was severe asthma exacerbations. The associated primary efficacy outcome variable was time to first severe asthma exacerbation. The number of severe asthma exacerbations was a secondary outcome variable
- Additional secondary efficacy variables were morning and evening peak expiratory flow (mPEF and ePEF), asthma symptom scores, nights with awakening(s) due to asthma symptom, inhalations of as-needed medication, asthma-control days, mild asthma exacerbation days, as-needed-free days, symptom-free days, FEV_1, overall treatment evaluation, and asthma quality of life questionnaire, standardised version (AQLQ(S)) overall and domain scores.

N.B. As-needed-free days and symptom-free days were added as variables to the statistical analyses to conform with previous Symbicort studies. It was done after finalisation of the study protocol, but before unblinding of study data.

Safety

Safety assessments including physical examination, adverse events (AEs), pulse and blood pressure, were obtained in all subjects. In two subgroups of subjects, following variables were obtained;

- electrocardiogram (ECG), haematology and clinical chemistry (including s-potassium), urine analysis, p-cortisol in approximately 400 subjects
- adrenal stimulation test (i.e. ACTH-test) in approximately 100 subjects.

The subjects in the subgroups came from a limited number of countries; France, Germany, the Netherlands, South Africa and Canada (only s-Potassium and ECG).

Statistical methods

The full analysis set, as defined in ICH guideline E9, was used in all efficacy and safety analyses.

Time to first severe asthma exacerbation was compared between treatments using a log-rank test. Additional descriptions were made using a Cox proportional hazards model with treatment as factor. The total number of severe asthma exacerbations was compared between treatments using a Poisson regression model with treatment as factor and the time in study as an offset variable. The confidence limits and the p-value were adjusted for overdispersion.

Time to first mild asthma exacerbation was analysed in the same way as time to first severe asthma exacerbation. Variables measured in diaries and at clinical visits were compared between treatments using analysis of variance models.

The safety variables were analysed by means of descriptive statistics and qualitative analysis.

Subject population

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

Variable	Symbicort SiT	Pulmicort	ALL
Total (N)	947	943	1890
Sex			
-Male	393	405	798
-Female	554	538	1092
Age (yrs)	43	43	43
	(12-79)	(11-80)	(11-80)
Age interval			
-11	0	1	1

(Continued)

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

Variable	Symbicort SiT	Pulmicort	ALL
12-17	56	64	120
18-64	814	806	1620
65-	77	72	149
Race			
-Caucasian	877	874	1751
-Black	4	5	9
-Oriental	6	7	13
-Other	60	57	117
Time since diagnosis (yrs) [1)]	12	12	12
	(1-65)	(1-71)	(1-71)
IGCS at entry (µg)	744	748	746
	(250-2000)	(400-2000)	(250-2000)
FEV_1 (L)	2.19	2.18	2.19
	(0.79-4.43)	(0.84-3.95)	(0.79-4.43)
FEV_1 (% P.N.)	70	70	70
	(46-102)	(37-95)	(37-102)
Reversibility (%)	24	24	24
	(7-152)	(7-171)	(7-171)
Mean no. of as-needed medication/24h	1.9	2.0	1.9
	(0.0-15.6)	(0.0-9.2)	(0.0-15.6)
As-needed-free days (%)	29	26	28
	(0-100)	(0-100)	(0-100)
Mean symptom score (0-6)	1.8	1.9	1.9
	(0.0-6.0)	(0.0-6.0)	(0.0-6.0)
Symptom-free days (%)	10	10	10
	(0-100)	(0-100)	(0-100)
Asthma-control days (%)	8	8	8
	(0-100)	(0-90)	(0-100)

1. Median

The overall impression of demography and baseline characteristics, was that the treatment groups were comparable.

Table S2. Disposition of subjects

Variable	Symbicort SiT (N)	Pulmicort (N)	All (N)
Randomised	947	943	1890
Discontinued	144	173	317
Completed	803	770	1573
Analyzed for efficacy	947	943	1890
Analyzed for safety	947	943	1890

There were slightly more subjects that discontinued in the Pulmicort group, but it was not statistically significant. The most common reason for discontinuation was eligibility criteria not fulfilled.

Efficacy results

Symbicort SiT was more efficacious than Pulmicort as demonstrated by an improvement in the primary outcome variable, time to first severe asthma exacerbation, ($p<0.001$). The Symbicort SiT group was also shown to be superior to the Pulmicort group with regards to mean number of severe asthma exacerbation per subject (0.30 vs 0.51 exacerbations/subject). Moreover, the total use of systemic steroids for treatment of severe asthma exacerbation was lower in the Symbicort SiT group than for Pulmicort (1776 vs 3177 treatment days). The results for secondary variables supported those of the primary variable. Symbicort SiT decreased the daily use of as-needed medication, increased morning and evening PEF, decreased the total daily asthma symptom score, reduced awakenings due to asthma symptoms, prolonged time to first mild asthma exacerbation, decreased the number of mild asthma exacerbation days, increased FEV_1, and had a more favorable overall treatment evaluation at Visits 3 and 7 compared with Pulmicort. In addition, Symbicort SiT increased the number of as-needed-free days, symptom-free days and asthma-control days compared with Pulmicort. AQLQ(S) scores were similar in the two treatment groups.

Table S3. Number of subjects with severe asthma exacerbations, total and by sub criteria

Event		Symbicort SiT	Pulmicort
	No of subjects	947	943
Severe asthma exacerbations (total)	No of subjects	170 (18%)	259 (27%)
	No of events	331	546
	Subjects with 1 event	108	140
	" with 2 events	35	54
	" with 3 events	17	34

(Continued)

Table S3. Number of subjects with severe asthma exacerbations, total and by sub criteria

Event	Symbicort SiT	Pulmicort
" with >3 event	10	31
Max events/subject	23	21

Table S4. Summary of result for primary efficacy variables

Variable		Treatment comparison	Estimate	95% Conf.Limits	P-value
Severe asthma exacerbation	- time to first[1]	Symbicort SiT vs. Pulmicort	NA	NA	<0.001
	- time to first[2]	Symbicort SiT vs. Pulmicort	0.61	(0.50, 0.74)	<0.001
	- events/subject[3]	Symbicort SiT	0.30	(0.26, 0.35)	
		Pulmicort	0.51	(0.46, 057)	
		Symbicort SiT vs. Pulmicort	0.59	(0.49, 0.71)	<0.001

1. Log-rank test
2. Cox PH model
3. Poisson regression

Safety results

The extent of exposure was similar for the two treatment groups, and there was no obvious difference in number of subjects reporting AEs for each category. The most frequently reported AE on a preferred term level, for both treatments, was respiratory infection. The AEs were mostly mild to moderate in intensity. There were three deaths reported in the study, two in the Pulmicort group and one in the Symbicort SiT group. None of the deaths were related to asthma or, as judged by the investigator causally related to investigational product. The number of non-fatal serious adverse events (SAEs) and discontinuations due to adverse event (DAEs) was low. Two non-fatal SAEs (dizziness and atrial fibrillation) in the Symbicort SiT group were considered by the investigator to be causally related to investigational product. The incidence of events associated with asthma, in terms of overall AE, SAE and DAE, was slightly lower in the Symbicort SiT group, when compared with the Pulmicort group. No other significant adverse events (OAEs) were identified in the study. The number of subjects shifting from normal at baseline to abnormal at end-of-treatment in clinical laboratory, ECG and vital signs variables was low and the number of treatment emergent laboratory changes (TELCs) were evenly distributed between the treatment groups. There was no statistically significant difference found between the treatment groups in mean morning plasma cortisol. Between Visit 2 to 7 there was a numerical increase in

ACTH-stimulated mean maximal plasma cortisol concentrations in the Symbicort SiT group, however there was no statistically significant difference when compared to Pulmicort.

Table S5. Summary of adverse events

Category of adverse event	Symbicort SiT N=947	Pulmicort N=943	Total N=1890
No. (%) of deaths	1(<0.5)	2(<0.5)	3 (<0.5)
No. of SAEs (non-fatal)	66	58	124
No. (%) of subjects with non-fatal SAEs	49(5%)	50(5%)	99(5%)
No. of other significant AEs	0	0	0
No (%) of DAEs	24(3%)	38(4%)	62(3%)
No. of AEs*	1252	1243	2495
Number of AEs per 1000 treatment days	4.0	4.1	4.1
No. (%) of subjects with AE	526(56%)	533(57%)	1059(56 %)

1. * events are counted by preferred term, i.e; for subjects with multiple events falling under the same preferred term, only one occurence of the event is counted.

Table S6. Adverse Events by preferred term. Number (%) of all subjects with the most commonly reported AEs, sorted by decreasing order of frequency as summarized over all treatment groups. (Only 10 most frequently reported AEs are listed).

Preferred term	Symbicort SiT N = 947	Pulmicort N = 943	All N = 1890
Respiratory infection	172(18%)	177(19%)	349(18%)
Pharyngitis	68(7%)	69(7%)	137(7%)
Bronchitis	63(7%)	72(8%)	135(7%)
Rhinitis	69(7%)	56(6%)	125(7%)
Sinusitis	44(5%)	49(5%)	93(5%)
Headache	42(4%)	47(5%)	89(5%)
Infection viral	37(4%)	36(4%)	73(4%)
Asthma aggravated	28(3%)	43(5%)	71(4%)
Accident and/or injury	34(4%)	34(4%)	68(4%)
Back pain	28(3%)	26(3%)	54(3%)