AstraZeneca

Drug product:	Budesonide/formoterol	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Budesonide/formoterol		
Document No.:	SD-039-CR-0673	Referring to part of the dossier	
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Efficacy and safety of budesonide/formoterol (Symbicort) Turbuhaler® as Single Therapy in patients with mild-moderate asthma. Comparison with Symbicort Turbuhaler and Pulmicort® Turbuhaler as maintenance therapy, both complemented with Bricanyl® Turbuhaler (STAY).

Study centre(s)

This was a multicentre study with 246 centres participating from the following countries: Argentina (10 centres), Brazil (10 centres), Bulgaria (7 centres), Canada (30 centres), China (5 centres), France (26 centres), Great Britain (21 centres), Hungary (17 centres), Indonesia (4 centres), Israel (16 centres), Italy (13 centres), Malaysia (3 centres), Mexico (5 centres), Norway (13 centres), The Philippines (10 centres), Poland (11 centres), Romania (7 centres), Singapore (3 centres), South Africa (11 centres), Sweden (6 centres), Taiwan (6 centres) and Turkey (12 centres).

Publications

None at the time of finalising this report.

Clinical Study Report Synopsis Document No. SD-039-CR-0673 Edition No. 2.0 Study code SD-039-0673	(For national authority use only)

Study dates:

First subject enrolled 15 January, 2001

Last subject completed 30 January, 2003

Phase of Development

Therapeutic confirmatory (III)

Objectives

The *primary objective* of the study was to compare the efficacy of the regular use of Symbicort Turbuhaler 80/4.5 µg bid, complemented by the as-needed use of the same product with the same dosage of Symbicort complemented with Bricanyl Turbuhaler 0.4 mg as-needed.

One *secondary objective* of the study was to compare the efficacy of Symbicort Turbuhaler 80/4.5 µg bid, complemented by the as-needed use of the same product, with Pulmicort® Turbuhaler® 320 µg bid (i.e. a four times higher steroid dose) complemented with Bricanyl Turbuhaler 0.4 mg as-needed.

Safety was also a *secondary objective*. The safety of Symbicort Turbuhaler 80/4.5 µg/inhalation, 1 inhalation bid plus Symbicort Turbuhaler 80/4.5 µg/inhalation as-needed, was compared with Symbicort Turbuhaler 80/4.5 µg/inhalation, 1 inhalation bid plus Bricanyl Turbuhaler 0.4 mg/inhalation as-needed or Pulmicort Turbuhaler 320 µg/inhalation, 1 inhalation bid plus Bricanyl Turbuhaler 0.4 mg/inhalation as-needed. The evaluation of safety took into account several safety variables with no particular variable being chosen as the main safety variable.

For the subject group 4-11 years half the regular dose was given, administered once daily in the evening.

Study design

The study was double-blind, randomized, active-controlled, multicentre and multi-national with a parallel group design comparing the efficacy and safety of Symbicort 80/4.5 µg/inhalation, 1 inhalation twice daily plus Symbicort 80/4.5 µg/inhalation as-needed (Symbicort single-inhaler therapy, SiT) with that of Symbicort 80/4.5 µg/inhalation, 1 inhalation twice daily plus Bricanyl 0.4 mg/inhalation as-needed and Pulmicort 320 µg/inhalation, 1 inhalation twice daily plus Bricanyl 0.4 mg/inhalation as-needed when given for a period of 12 months for the treatment of asthma.

For the subject group 4-11 years half the regular dose was given, administered once daily in the evening.

Target subject population and sample size

Male and female subjects, 4-80 years of age, with asthma, previously treated with 400-1000 µg inhaled glucocorticosteroids (IGCS; 200-500 µg for subjects 4-11 years) were included. Inclusion criteria included a forced expiratory volume in one second (FEV_1) of 60-90% of predicted normal value and ≥12 % reversibility in FEV_1. The subjects had to have used at least 12 inhalations (8 inhalations for subjects 4-11 years) of their as-needed medication during the last 10 days of the run-in period.

After an amendment dated 27 April 2001 subjects aged 4-11 years were allowed to have a FEV_1 of 60-100% of predicted normal value instead of 60-90%.

Assuming the true incidence of asthma exacerbations in one of the groups to be 25%, a sample size of 800 randomized subjects per group results in 80% probability to detect a true reduction 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 products: dosage, mode of administration and batch numbers

Symbicort (budesonide/formoterol fumarate dihydrate) 80/4.5 µg/inhalation, 1 inhalation bid + Symbicort 80/4.5 µg/inhalation as-needed, Symbicort 80/4.5 µg/inhalation, 1 inhalation bid + Bricanyl (terbutaline suphate) Turbuhaler® 0.4 mg/inhalation as-needed or Pulmicort (budesonide) 320 µg/inhalation, 1 inhalation bid + Bricanyl Turbuhaler® 0.4 mg/inhalation as-needed.

The randomization was stratified in two age groups, 4-11 years and 12-80 years. For the subject group 4-11 years half the regular dose was given, administered once daily in the evening.

Doses were given in two inhalers identical between treatments, i.e. inhalers for regular treatment (Symbicort or Pulmicort) were identical and inhalers for as-needed use (Symbicort or Bricanyl) were identical. Batch numbers were: Symbicort BF14, BF15, BH17, CC18; Pulmicort BF11, CD12; Bricanyl BG21-24, BL26, CC27-30, CI32.

The treatment arm with Symbicort, both as regular treatment and as-needed, will be referred to as Symbicort SiT, the treatment arm with Symbicort as regular treatment and Bricanyl as-needed will be referred to as Symbicort and the treatment arm with Pulmicort as regular treatment and Bricanyl as-needed will be referred to as Pulmicort.

Duration of treatment

The study included a 2-week run-in period followed by a 12-month treatment period.

Criteria for evaluation (main variables)

Efficacy

The primary efficacy variable was severe asthma exacerbations. The associated primary efficacy outcome variable was time to first severe asthma exacerbation. Number of severe asthma exacerbations was a secondary outcome variable.

Secondary efficacy variables were morning and evening peak expiratory flow (PEF), asthma symptom scores, nights with awakening(s) due to asthma symptoms, inhalations of as-needed medication, asthma-control days, mild asthma exacerbation days, mild asthma exacerbations, FEV_1, Asthma Quality of Life Questionnaire, standardized version (AQLQ(S)) score, Paediatric Asthma Quality of Life questionnaire, standardized version (PAQLQ(S)) score, Asthma Symptom Utility Index (ASUI) score, overall treatment evaluation, health care resource utilisation, sick-leave and work productivity and activity impairment. To conform with previous Symbicort studies as-needed-free days and symptom-free days were added as variables to the statistical analyses. This was done before unblinding of study data.

Safety

The following safety variables were to be assessed in all subjects: physical examination, pulse, blood pressure and adverse events (AEs).

ECG, haematology, clinical chemistry (including s-potassium), urinalysis, ACTH test and p-cortisol was measured in subgroups of subjects.

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 categorical data, frequencies are given, for other data mean values and ranges are given

		Symbicort SiT	Symbicort	Pulmicort	ALL
Population					
N randomized		925	909	926	2760
Demographic characteristics					
Sex (N)	Male	421	394	416	1231
	Female	504	515	510	1529
Age (yrs)	Mean	35	36	36	36
	Range	(4-77)	(4-79)	(4-79)	(4-79)
Age interval (N)	-11	118	117	106	341
	12-17	106	103	107	316
	18-64	645	631	652	1928
	65-	56	58	61	175
Race	Caucasian	712	707	711	2130
	Black	7	9	13	29
	Oriental	149	148	158	455
	Other	57	45	44	146
Time since diagnosis (yrs)	Median	9	9	9	9
	Range	(0-63)	(0-65)	(0-69)	(0-69)
IGCS at entry (µg/day)	Mean	619	598	620	612
	Range	(200-1200)	(200-1000)	(100-1000)	(100-1200)
Baseline characteristics					
FEV_1 (L)	Mean	2.13	2.10	2.14	2.12
	Range	(0.65-4.28)	(0.62-4.50)	(0.64-4.02)	(0.62-4.50)
FEV_1 (% PN)	Mean	73	73	73	73
	Range	(43-108)	(46-108)	(49-100)	(43-108)
Reversibility (%)	Mean	21	21	21	21
	Range	(2-89)	(12-75)	(3-77)	(2-89)
Mean no of as-needed taken/24 h	Mean	2.5	2.4	2.4	2.4
	Range	(0.0-9.3)	(0.0-13.5)	(0.0-8.1)	(0.0-13.5)
Mean symptom score (0-6)	Mean	1.5	1.4	1.5	1.5
	Range	(0.0-6.0)	(0.0-5.2)	(0.0-5.6)	(0.0-6.0)
Disposition					
N of subjects	Completed	800	758	783	2341

(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

		Symbicort SiT	Symbicort	Pulmicort	ALL
	Discontinued	122	148	142	412
	Not treated or no data on treatment	3	3	1	7
N analysed for safety		922	906	925	2753
N analyzed for efficacy (ITT)		922	906	925	2753

• FEV_1 forced expiratory volume in one second; IGCS inhaled glucocorticosteroids; ITT intention to treat; N number; PN predicted normal

Table S2. Treatment group comparison of demographic and disease data for the age group 4-11 years. For categorical data, frequencies are given, for other data mean values and ranges are given

		Symbicort SiT	Symbicort	Pulmicort	ALL
Population					
N randomized		118	117	106	341
Demographic characteristics					
Sex (N)	Male	85	82	70	237
	Female	33	35	36	104
Age (yrs)	Mean	8	8	8	8
	range	(4-11)	(4-11)	(4-11)	(4-11)
Inhaled GCS at entry	Mean	319	302	321	314
	Range	(200-500)	(200-500)	(100-500)	(100-500)
Baseline characteristics					
FEV_1 (L)	Mean	1.46	1.36	1.44	1.42
	Range	(0.65-2.33)	(0.62-2.41)	(0.64-2.77)	(0.62-2.77)
FEV_1 (% PN)	Mean	76	76	76	76
	Range	(57-108)	(54-99)	(60-100)	(54-108)
Reversibility (%)	Mean	23	24	23	23
	Range	(12-89)	(12-70)	(11-58)	(11-89)
Mean no of as-needed taken/24 h	Mean	1.7	1.6	1.6	1.6
	Range	(0.7-5.9)	(0.3-5.6)	(0.1-4.0)	(0.1-5.9)
Mean symptom score (0-6)	Mean	1.1	1.1	1.2	1.1
	Range	(0.0-4.4)	(0.0-3.5)	(0.0-3.4)	(0.0-4.4)

• FEV_1 forced expiratory volume in one second; GCS glucocorticosteroids; N number; PN predicted normal

The treatment groups were generally well balanced in demographic and baseline characteristics. Discontinuations of study treatment were relatively rare in all treatment groups.

Efficacy results

Symbicort SiT was shown to be more efficacious than both Symbicort and Pulmicort in the treatment of persistent asthma over a 12-month treatment period as demonstrated by an improvement in the primary outcome variable, time to first severe asthma exacerbation, ($p<0.001$ for both comparisons). The Symbicort SiT group was also shown to be superior to both Symbicort and Pulmicort with regards to mean number of severe asthma exacerbations per subject (0.29 vs 0.54 and 0.54 exacerbations/subject). Moreover, the total use of systemic steroids was lower in the Symbicort SiT group than in both the Symbicort and Pulmicort

groups (1255 vs 2918 and 2577 treatment days, respectively). 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 the time to first mild asthma exacerbation, decreased the number of mild asthma exacerbation days, increased FEV_1, increased AQLQ(S), increased ASUI and had a more favourable overall treatment evaluation at Visit 7 as compared to Symbicort and Pulmicort. In addition, the number of as-needed-free days, symptom-free days and asthma-control days was increased and the overall treatment evaluation at Visit 3 was more favourable with Symbicort SiT compared to Pulmicort. The results in subjects 4-11 years of age were similar to the results in the full population. For the primary outcome variable, time to first severe asthma exacerbation, Symbicort SiT was shown to be superior to the other treatments in this age group.

Table S3 shows the number of subjects with severe asthma exacerbations and Table S4 the statistical analysis. Tables S5 and S6 shows the same data for subjects aged 4-11 years.

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

Event		Symbicort SiT	Symbicort	Pulmicort
	N of subjects	922	906	925
Severe asthma exacerbations	N of subjects	148 (16%)	248 (27%)	256 (28%)
(Total)	N of events	303	553	564
	Subjects with 1 event	96	127	139
	Subjects with 2 events	31	50	57
	Subjects with 3 events	6	34	27
	Subjects with >3 event	15	37	33
	Max events/subject	28	17	34

- N number

Table S4. Statistical analysis of severe asthma exacerbations.

Variable	Analysis	Treatment	estimate	95% conf.int.	P-value
-Time to first	Log-rank test	Symbicort SiT vs. Symbicort			<0.001
		Symbicort SiT vs. Pulmicort			<0.001
		Symbicort vs. Pulmicort			0.74
	Cox PH model	Symbicort SiT vs. Symbicort	0.55	(0.44, 0.67)	<0.001

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Table S4. Statistical analysis of severe asthma exacerbations.

Variable	Analysis	Treatment	estimate	95% conf.int.	P-value
		Symbicort SiT vs. Pulmicort	0.53	(0.43, 0.65)	<0.001
		Symbicort vs. Pulmicort	0.97	(0.82, 1.16)	0.74
-Events/subject	Poisson regression	Symbicort SiT	0.29	(0.25, 0.34)	
		Symbicort	0.54	(0.48, 0.61)	
		Pulmicort	0.54	(0.48, 0.61)	
		Symbicort SiT vs. Symbicort	0.53	(0.44, 0.65)	<0.001
		Symbicort SiT vs. Pulmicort	0.53	(0.44, 0.64)	<0.001
		Symbicort vs. Pulmicort	1.00	(0.85, 1.17)	0.98

• PEF peak expiratory flow

Table S5. Number of subjects in the age group 4-11 years with severe asthma exacerbations, total and by sub criteria

Event		Symbicort SiT	Symbicort	Pulmicort
	N of subjects	118	117	106
Severe asthma exacerbations	N of subjects	17 (14%)	44 (38%)	28 (26%)
(Total)	N of events	54	100	55
	Subjects with 1 event	12	26	15
	Subjects with 2 events	2	7	5
	Subjects with 3 events	0	3	5
	Subjects with >3 event	3	8	3
	Max events/subject	28	14	7

• N number

Table S6. Statistical analysis of severe asthma exacerbations in the age group 4-11 years.

Variable	Analysis	Treatment	estimate	95% conf.int.	P-value
-Time to first	Log-rank test	Symbicort SiT vs. Symbicort			<0.001
		Symbicort SiT vs. Pulmicort			0.02
		Symbicort vs. Pulmicort			0.12
	Cox PH model	Symbicort SiT vs. Symbicort	0.34	(0.19, 0.60)	<0.001
		Symbicort SiT vs. Pulmicort	0.49	(0.27, 0.90)	0.022
		Symbicort vs. Pulmicort	1.45	(0.90, 2.33)	0.12
-Events/subject	Poisson regression	Symbicort SiT	0.41	(0.28, 0.62)	
		Symbicort	0.76	(0.57, 1.02)	
		Pulmicort	0.48	(0.33, 0.72)	
		Symbicort SiT vs. Symbicort	0.55	(0.33, 0.90)	0.017
		Symbicort SiT vs. Pulmicort	0.86	(0.49, 1.50)	0.59
		Symbicort vs. Pulmicort	1.57	(0.96, 2.57)	0.073

• PEF peak expiratory flow

Safety results

The extent of exposure was similar for the three 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 all treatments, was respiratory infection. For the age group 4-11 years, the most frequently reported AE was pharyngitis. The incidence of asthma aggravated was lowest in the Symbicort SiT group, both within the total study population and in the subgroup of children. For the age group 4-11 years, the incidence of adverse events associated with asthma was higher in the Symbicort group than in the Pulmicort group receiving a 4-fold higher dose of budesonide. No other clinically important differences across the treatment groups were observed with regard to the nature, incidence or severity of adverse events. The number of serious adverse events and discontinuations due to adverse events was low in all treatment groups. There were 3 deaths reported in the study, 2 in the Symbicort group and 1 in the Pulmicort group. None of the deaths were, judged by the investigator to be, causally related to the investigational product. One of

the deaths was due to acute respiratory failure secondary to severe asthma exacerbation (Symbicort group). Four non-fatal SAEs were considered by the investigator to be causally related to the investigational product. One SAE was in the Symbicort SiT group (acute oedema of epiglottis) and three were in the Symbicort group (severe asthma exacerbation, limb pain, worsening of asthma). Sixty-seven subjects (14 in the Symbicort SiT group, 29 in the Symbicort group and 24 in the Pulmicort group) discontinued due to AEs. No OAEs were identified in the study. In adults (12-80) in the Pulmicort group, there was a numerical decrease in mean morning plasma cortisol between Visit 2 and Visit 7 compared with the other groups, however, the differences between the groups were not statistically significant. Apart from this, no clinically important differences between the treatment groups, or changes over time, were identified with regard to clinical laboratory (including mean morning plasma cortisol), vital signs or ECG measurements. In the age group 4-11 years, effects upon adrenal function within the Symbicort SiT group and Symbicort group were less than those seen within the Pulmicort group. Furthermore, children in the Symbicort SiT group and Symbicort group displayed significantly greater longitudinal growth than those in the Pulmicort group. No other clinically important differences between the treatment groups or changes over time were identified in children with regard to clinical laboratory (including mean morning plasma cortisol) or vital signs measurements.

Table S7. Number (%) of subjects who had an adverse event in any category (safety population)

	Symbicort SiT	Symbicort	Pulmicort	Total
No. of subjects	922	906	925	2753
Category of adverse event				
No. of deaths	0	2	1	3
No. of SAEs (non-fatal)	62	73	62	197
No. (%) of subjects with non-fatal SAEs	46(5%)	60(7%)	47(5%)	153(6%)
No. of SAE cases in the Safety database (fatal and non-fatal) [a]	52	66	55	173
No. of other significant AEs	0	0	0	0
No. (%) of DAEs	14(2%)	29(3%)	24(3%)	67(2 %)
No. of AEs[b]	1115	1136	1253	3504
No. of AEs/1000 treatment days	3.6	3.8	4.1	3.8
No. (%) of subjects with AE	496(54%)	475(52%)	528(57%)	1499(54 %)

a. Data derived from the safety data base. In one SAE case, more than one AE reported as serious can be included.

b. Events are counted by preferred term, ie; for subjects with multiple events falling under the same preferred term, only one occurrence of the event is counted.

AE adverse event; DAE discontinuations due to adverse event; SAE serious adverse event

Table S8. 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. The 10 most frequently reported AEs are presented

	Symbicort SiT	Symbicort	Pulmicort	All
No. of subjects	922	906	925	2753
Preferred term				
Respiratory infection	158(17%)	144(16%)	182(20%)	484(18%)
Pharyngitis	88(10%)	88(10%)	86(9%)	262(10%)
Rhinitis	80(9%)	72(8%)	76(8%)	228(8%)
Bronchitis	51(6%)	61(7%)	76(8%)	188(7%)
Sinusitis	43(5%)	39(4%)	33(4%)	115(4%)
Headache	31(3%)	35(4%)	42(5%)	108(4%)