AstraZeneca

Drug product:	Symbicort® Turbuhaler®	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Budesonide/formoterol		
Document No.:	SD-039-CR-0686	Referring to part of the dossier	
Edition No.:	1		
Study code:	SD-039-0686		
Date:	17 April, 2003		

A randomized, double-dummy, double-blind/open, parallel-group, phase-III, multicentre, 7-month study to assess the efficacy and safety of Symbicort® Turbuhaler® (budesonide/formoterol; 160/4.5 µg delivered dose) given either as standard therapy (2 inhal. b.i.d.) or with an adjustable dosing regimen (1, 2 or 4 inhal. b.i.d.) versus Seretide™ Diskus™ (salmeterol/fluticasone; 50/250 µg metered dose) given as standard therapy (1 inhal. b.i.d.) in adult and adolescent asthmatic patients

Study centre(s)

The study was conducted in Denmark (9 centres), Finland (10 centres), Germany (11 centres), the Netherlands (12 centres), Norway (41 centres), and Sweden (10 centres).

Publications

3 abstracts submitted to ICACI, Vancouver, Sept 2003 (Aalbers R., Backer V., Kava T., Welte T., Omenaas E., Bergqvist P.B.F., and Sandström T.):

- Adjustable dosing with budesonide/formoterol reduces the rate of asthma exacerbations compared with fixed dosing salmeterol/fluticasone
- Improvements in FEV_1 are greater with budesonide/formoterol than with salmeterol/fluticasone

- Is well-controlled asthma weeks a useful measure? Fewer exacerbations in patients treated with budesonide/formoterol than salmeterol/fluticasone

Study dates:

First subject enrolled 10 October, 2001

Last subject completed 21 December, 2002

Phase of Development

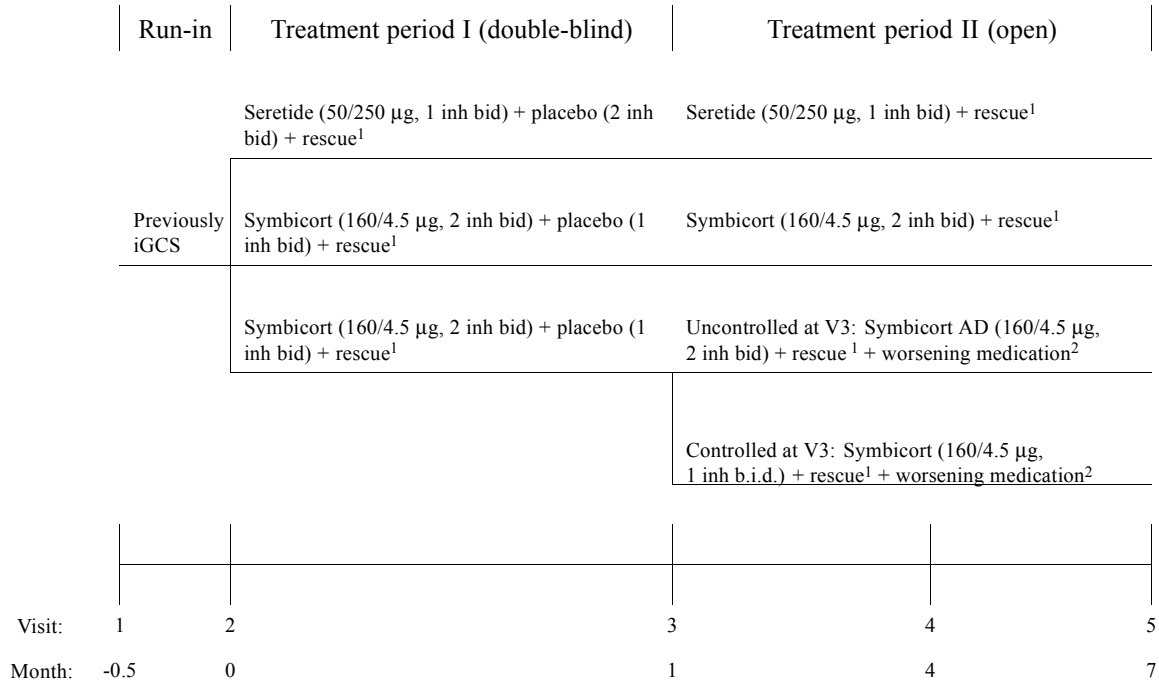
Therapeutic confirmatory (III)

Objectives

The **primary objective** of the study was to compare the efficacy of Symbicort Turbuhaler, given as a standard therapy or with an adjustable dosing regimen, with that of Seretide Diskus given as a standard therapy in asthmatic adults and adolescents.

The **secondary objective** was to study safety of the treatments.

Study design



1. Short-acting β_2-agonist.
2. Addition of Symbicort 160/4.5 µg up to 4 inhal bid during asthma worsening.

This was a randomized, double-dummy, double-blind/open, parallel-group, multicentre, 7-month study comparing the efficacy and safety of Symbicort (budesonide/formoterol; 160/4.5 µg delivered dose) given either as standard therapy (2 inhalations morning and evening) or with an adjustable dosing regimen (1 or 2 inhalations morning and evening, with an increase to 4 inhalations morning and evening for 7-14 days in case of asthma worsening according to an asthma control plan) versus Seretide (salmeterol/fluticasone; 50/250 µg metered dose) given as standard therapy (1 inhalation morning and evening) in adult and adolescent asthmatic patients using inhaled glucocorticosteroids (GCSs).

Target subject population and sample size

Male or female subjects aged ≥12 years with a diagnosis of perennial asthma, using ≥500 - ≤1200 µg daily of inhaled GCS, with a forced expiratory volume in one second (FEV_1) ≥50% of predicted normal. The subjects must have had a total asthma symptom score ≥1 on at least 4 of the last 7 days of the run-in period and a mean morning peak expiratory flow (PEF) during the last 7 days of the run-in period of >50 and <85% of postbronchodilatory PEF measured at Visit 1 or 2. The subjects should not have experienced any asthma exacerbation or have taken oral, rectal or parenteral GCSs within 1 month prior to Visit 1.

Based on a previous study, with 200 completed subjects per treatment group, an actual difference of 8.5% between two groups could be detected with 80% power (assuming a significance level of 5% and a 2-sided alternative hypothesis).

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

- Seretide Diskus (salmeterol/fluticasone), 50/250 µg per inhalation, 1 inhalation morning and evening during the complete study period, batches no. 139 and B043876
- Symbicort Turbuhaler (budesonide/formoterol), 160/4.5 µg per inhalation, 2 inhalations morning and evening during the complete study period, batch no. CD 27
- Symbicort Turbuhaler Adjustable Dosing (Symbicort AD), 160/4.5 µg per inhalation, 2 inhalations morning and evening during the first part (1 month; Treatment period I) of the study and thereafter either 1 or 2 inhalations morning and evening (with an increase to 4 inhalations morning and evening for 7-14 days in case of asthma worsening) during the second part (6 months; Treatment period II) of the study, batch no. CD 27

Duration of treatment

The run-in period was 10-14 days and the randomized treatment period was 7 months long.

Criteria for evaluation (main variables)

Efficacy

- The primary efficacy endpoint was the odds of having a well-controlled asthma week during the randomized treatment period.
- The secondary efficacy endpoints were:
    - the proportion of subjects with well-controlled asthma weeks during both the last 2 weeks of Treatment period I
    - the odds of having a week with total asthma control during the randomized treatment period
    - number of exacerbations per subject during the randomized part of the study
    - time to first exacerbation
    - change in FEV_1 from Visit 2 to the average of Visits 3 and 5
    - change in average morning and evening PEF from run-in to the randomized part of the study
    - change in average daytime and night-time symptom score from run-in to the randomized part of the study
    - change in average number of occasions of rescue medication use from run-in to the randomized part of the study

Safety

The incidence, severity, and type of adverse events (AEs).

Statistical methods

The full analysis set was used in all efficacy and safety analyses.

The incidence of well-controlled asthma weeks during the treatment period was considered as a series of correlated binary variables. A generalized estimating equation (GEE) with a logistic link function, the dependency model as exchangeable observations, treatment, country and asthma control the last week before randomization (well-controlled or not) as factors and subject as cluster were used to estimate the odds of having a well-controlled asthma week and to compare the treatments. Number of exacerbations were analysed in a Poisson regression model and time to first exacerbation was analysed in a COX proportional hazards model. Period means of diary card variables and FEV_1 were analysed in ANOVA models adjusting for run-in and country.

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

Subject population

Table S1. Subject population and disposition

		Seretide	Symbicort	Symbicort AD	ALL
N enrolled					1044
N randomized (planned)		224 (200)	215 (200)	219 (200)	658 (600)
Sex (n)	Male	109	96	94	299 (45%)
	Female	115	119	125	359 (55%)
Age (years)	Mean (range)	46 (14-78)	46 (13-85)	47 (12-76)	46 (12-85)
Age category (n)	12-17 years	4	4	7	15
	18-65 years	204	190	190	584
	>65 years	16	21	22	59
Race (n)	Caucasian				649
	Black				2
	Oriental				7
Inhaled GCS dose (µg)	Mean (range)	729 (400-1200)	751 (500-1600)	725 (500-1600)	735 (400-1600)
FEV_1 (L)	Mean (range)	2.78 (1.20-5.76)	2.70 (1.03-4.94)	2.71 (0.98-6.11)	2.73 (0.98-6.11)
FEV_1 (% predicted)	Mean (range)	85 (50-134)	84 (45-156)	84 (47-142)	84 (45-156)
N subjects who	completed	199	184	192	575
	discontinued	25	31	27	83
N analyzed for safety and efficacy		224	215	219	658

The overall impression is that the three treatment groups were comparable at baseline.

Efficacy results

Table S2. Summary of the efficacy results

Variable		Period		
		Randomized treatment (Double-blind+open period)		Double-blind period[1]
Comparison		Seretide vs Symbicort (primary comparison)	Seretide vs Symbicort AD	Seretide vs Symbicort
Primary variable	Well-controlled asthma weeks	No difference (odds ratio 1.289; p=0.069)	No difference (odds ratio 0.997; p=0.98)	No difference (odds ratio 1.210; p=0.35)[2]
Secondary variables	Total asthma control weeks	No difference (odds ratio 1.248; p=0.21)	No difference (odds ratio 1.146; p=0.44)	No difference (odds ratio 1.141; p=0.74)[2]
	Exacerbations	No difference (rate ratio 1.128; p=0.53)	A statistically significant reduction in number of exacerbations for the Symbicort AD group (rate ratio 1.658; p=0.018)	Not applicable
	FEV_1	FEV_1 increased more in the Symbicort group (diff. -58 mL; p=0.041)	No difference (diff. -8 mL; p=0.76)	FEV_1 increased more in the Symbicort group (diff. -50 mL; p=0.047)
	Morning PEF	No difference (diff. 0.9 L/min; p=0.81)	No difference (diff. 6.6 L/min; p=0.075)	No difference (diff. 2.7 L/min; p=0.32)
	Evening PEF	No difference (diff. -1.1 L/min; p=0.75)	Seretide significantly better (diff. 7.9 L/min; p=0.025)	No difference (diff. 1.3 L/min; p=0.62)
	Daytime symptom scores	No difference (diff. -0.05 score; p=0.43)	No difference (diff. 0.03 score; p=0.68)	No difference (diff. -0.00 score; p=0.97)
	Awakenings	No difference (diff. -1.7%; p=0.41)	No difference (diff. 2.5%; p=0.22)	No difference (diff. -2.3%; p=0.22)
	Rescue medication use	No difference (diff. -0.03 rescue occ. /24 h; p=0.79)	Symbicort AD significantly better (diff. 0.25 rescue occ. /24 h; p=0.0064)	No difference (diff. -0.1 rescue occ. /24 h; p=0.34)

1. The results of the Symbicort and Symbicort AD groups were pooled together.
2. The last 2 weeks of the double-blind period.

During the open period (i.e. Visit 3-5), the subjects in the Symbicort AD group used significantly less rescue medication than the Seretide subjects (diff. 0.23 rescue occ./24 h; p=0.011). Furthermore, the Seretide subjects had a significantly higher evening PEF than Symbicort AD (diff. 8.4 L/min; p=0.032).

Safety results

The mean exposure time was slightly lower in the Symbicort arm. Overall, the proportions of subjects reporting any AE were similar across the treatment groups; Symbicort 58%, Symbicort AD 57%, and Seretide 66%. The AEs were mostly of mild to moderate intensity, 92%.

The system organ class (SOC) in which most AEs were reported was Respiratory system disorders and in this SOC, Respiratory infection was the most frequently reported AE with a similar incidence across treatments. The incidence of dysphonia was slightly higher in the Seretide group compared to Symbicort treatment group and Symbicort AD group. A low incidence of moniliasis was observed in all treatment groups, Symbicort 1.9%, Symbicort AD 0.9%, and Seretide 3.1%. Asthma related AEs were similarly distributed across the treatment groups.

No deaths occurred during the course of the study. The proportion of subjects reporting serious adverse events (SAEs), other than death, was similar in the treatment groups. No SAEs were considered by the investigator to be causally related to the investigational product.

The frequency of subjects reporting discontinuations due to adverse events (DAEs) was similar between all treatment groups. The nature of DAEs showed no apparent treatment related distribution.