AstraZeneca

DRUG PRODUCT	Symbicort Turbuhaler	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide/Formoterol	REFERRING TO PART	
DOCUMENT NO.	SD-039-CR-0666	OF THE DOSSIER	
VERSION NO.	01		
STUDY CODE	SD-039-0666		
DATE	10 October, 2000		

FINAL

Symbicort High Dose Once Daily in Mild to Moderate Asthmatic Patients

STUDY CENTRES

The study involved 56 active centres in 9 countries; Argentina (5), Belgium (5), the Czech Republic (14), Germany (6), Mexico (4), Russia (6), Spain (5), the Netherlands (7) and United Kingdom (4).

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT ENROLLED	26 October, 1999	IIIA
- DATE OF LAST PATIENT COMPLETED	19 June, 2000	

PUBLICATION (REFERENCE)

OBJECTIVES

The primary objective was to compare the efficacy of Symbicort 160/4.5 μg, 2 inhalations given once daily in the evening with that of Pulmicort 400 μg given once daily in the evening, and Symbicort 160/4.5 μg given twice daily over a twelve-week treatment period.

The secondary objective was to study the safety of Symbicort given once daily.

STUDY DESIGN

This was a double-blind, double-dummy, randomised, active-controlled, multicentre study with a parallel-group design in GCS-using asthmatic adults.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Inclusion criteria: Out-patients (men or women), aged 18 years and older with perennial asthma (ATS) with a minimum duration of 6 months. Baseline FEV_1 of 60-90% of predicted normal. Reversibility in $FEV_1 \geq 12\%$ of baseline. Daily usage of 400-1000 μg inhaled GCSs (dose fixed for 30 days prior to inclusion). Written informed consent.
Exclusion criteria: Use of oral, parental or rectal GCS within 30 days prior to visit 1. Seasonal asthma. Significant respiratory infection within 30 days of visit 1. Severe cardiovascular disorder or any other significant disease or disorder. Women who were pregnant, breast-feeding or planning a pregnancy or not using acceptable contraceptives, or were not surgically sterile. Hypersensitivity to study drugs. Tobacco smokers or previous smokers if ≥10 pack-years. β-blocker therapy. Donation of blood. Planned surgery. Participation in a clinical study within 30 days prior to visit 1. Previously randomised into this study.
Randomisation criteria: Ability to use PEF meter and complete diary card correctly. Baseline diary data (morning PEF data) recorded on at least 7 (any 7) of the last 10 days prior to visit 2.

Criteria for discontinuation: Incorrect inclusion. Need for change in asthma therapy. Need for β-blocker therapy. Use of inhaled, oral (other than study medication), parenteral, or rectal GCS. Non-compliance. Pregnancy.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Symbicort (budesonide/formoterol) Turbuhaler® 160/4.5 μg 2 inhalations once daily by inhalation. Batch No: AF 19 and ZM 16

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Pulmicort (budesonide) Turbuhaler® 400 μg once daily by inhalation. Batch No: AD 651 and AK 669

Symbicort (budesonide/formoterol) Turbuhaler® 160/4.5 μg twice daily by inhalation. Batch No: AF 19 and ZM 16

DURATION OF TREATMENT

The study started with a 2-week run-in period and was followed by a 12-week treatment period.

MAIN VARIABLE(S):

- **EFFICACY**

The primary efficacy variable was morning peak expiratory flow (mPEF, L/min). Secondary variables included evening PEF, asthma symptoms, short-acting β_2-agonist use day and night and awakenings as recorded in diary cards. Lung function measurements (FEV_1 and FVC) were performed at each clinic visit.

- **SAFETY**

Safety was assessed on the basis of adverse events.

STATISTICAL METHODS

The primary analysis was an intention-to-treat analysis, including all randomised patients who received at least one dose of study medication. The primary efficacy variable was morning PEF as recorded by the patients in diary cards. Averages of existing values were calculated for the diary card variables for the last 10 days of the run-in period and for the whole of the treatment period. The change from run-in to the treatment period in these averages was analysed with an ANOVA model with factors treatment, country and their interaction and with the run-in average as covariate. Treatment contrasts were weighted over countries according to precision. The stability of the main results was assessed by the use of influential statistics. Time to first exacerbation was compared between groups using a logrank test. The primary comparison was between the once daily treatments with Symbicort Turbuhaler and Pulmicort Turbuhaler.

PATIENTS

Approximately 550 patients were to be enrolled (and 450 randomised) to reach at least 390 evaluable patients (130 in each arm). At least 8 patients were to be randomised per centre.

	Symbicort QD	Symbicort b.i.d.	Pulmicort	Total
No. planned (rand)	150	150	150	450
No. randomised and treated	176	176	171	523
Males/Females	67/109	64/112	68/103	199/324
Mean age (range)	42.7 (18-77)	44.8 (18-74)	45.5 (18-78)	44.3 (18-78)
Baseline values				
Mean iGCS dose (μg)	592	626	616	611
Mean FEV_1 (%predicted)	77.1 (44-126)	77.6 (43-111)	77.6 (33-132)	77.4 (33-132)
Mean reversibility (%)	21.5 (12-99)	21.2 (11-77)	22.6 (12-78)	21.8 (11-99)
No. analysed for efficacy	176	176	171	523
No. analysed for safety	176	176	171	523
No. completed	162	161	157	480

SUMMARY

- EFFICACY RESULTS

In terms of morning peak expiratory flow (mPEF, primary variable), both Symbicort treatments showed higher efficacy than Pulmicort as seen in the table below (estimated treatment contrasts).

	Contrast	Mean	95% CL	P-value
Change in morning PEF (L/min)	Symbicort QD vs Pulmicort QD	27.41	20.15 - 34.66	<0.001
	Symbicort bid vs Pulmicort QD	22.80	15.53 - 30.08	<0.001
	Symbicort QD vs Symbicort bid	4.60	-2.59 - 11.80	n.s.

Also for evening peak expiratory flow (ePEF), change in β_2-agonist use, symptom free days, rescue use free days and asthma control days, both Symbicort treatments showed better effect than Pulmicort. With regard to asthma symptoms sum score and night-time awakenings due to asthma, only the once-daily regimen of Symbicort showed better effect than Pulmicort.

When comparing the two Symbicort treatments with regard to ePEF, the twice daily regimen showed a somewhat higher efficacy. Still, both Symbicort treatments were better than Pulmicort also for this parameter. For the other variables mentioned above, no difference were shown between the two Symbicort treatments.

For the measurements made by spirometry at clinic visits, FEV_1 and FVC both Symbicort treatments showed superiority over Pulmicort for FEV_1, but only the twice-daily regimen with Symbicort over Pulmicort regarding FVC. Also here, there was no difference between the two Symbicort regimens.

- **SAFETY RESULTS**

The AEs showed a similar distribution between treatment groups.

One death was reported in the study.

Four SAEs other than the death were reported during randomised treatment, all of which were considered unrelated to treatment. The total number of SAEs was small and evenly distributed across the treatment groups.

In total 26 DAEs were reported during the study; 14 discontinued due to disease under study deteriorated and 12 discontinued due to other AEs, with even distribution across the treatment groups.