AstraZeneca

DRUG PRODUCT	Symbicort Turbuhaler	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide/Formoterol	REFERRING TO PART	
DOCUMENT NO.	SD-039-CR-0671	OF THE DOSSIER	
VERSION NO.	01		
STUDY CODE	SD-039-0671		
DATE	09 November, 2000		

FINAL

Efficacy of Symbicort Turbuhaler® compared with fluticasone Diskus™ in asthmatic patients not using steroids

STUDY CENTRE(S)

The study involved 32 active centres in 7 countries; Taiwan (1), Thailand (3), Vietnam (2), Israel (5), South Africa (6), Mexico (7) and Brazil (8).

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT ENROLLED	24 Nov 1999	IIIB
- DATE OF LAST PATIENT COMPLETED	26 July 2000	

PUBLICATION (REFERENCE)

OBJECTIVES

The primary objective was to compare the efficacy of Symbicort Turbuhaler, 80/4.5 μg b.i.d. with that of fluticasone Diskus, 250 μg b.i.d. over a 2-week treatment period. The secondary objective was to evaluate safety.

STUDY DESIGN

This was a double-blind, double-dummy, randomised, multicentre study with a parallel group design in patients with mild asthma not treated with inhaled corticosteroids (GCS).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Inclusion criteria: Out-patients of either gender ≥ 18 years. Perennial asthma diagnosis. Forced expiratory volume in one second (FEV_1) ≥70 - ≤100% of predicted normal. Reversibility in FEV_1 ≥12% of baseline. Signed informed consent.

Exclusion criteria: Oral, inhaled, parenteral or rectal GCS within 30 days prior to visit 1. Respiratory infection within 30 days prior to visit 1. Significant disease or disorder. Pregnancy. Hypersensitivity to study drugs. Smoking history of ≥10 pack-years. β-blocker therapy. Blood donation. Planned surgery.

Randomisation criteria: Ability to use Peak Expiratory Flow (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 oral, inhaled (other than study medication), parenteral, or rectal GCS. Non-compliance. Pregnancy.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Symbicort (budesonide/formoterol) Turbuhaler 80/4.5 μg, one inhalation twice daily. Batch No: AF 26.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Fluticasone Diskus 250 μg, one inhalation twice daily. Batch No: WP 306T and WP 31KR.

DURATION OF TREATMENT

After a 2-week run-in period during which baseline data were collected, the patients were randomised to a 2-week double-blind treatment period.

MAIN VARIABLE(S):

- **EFFICACY**

The primary efficacy variable was change in morning Peak Expiratory Flow (mPEF) (L/min) from baseline to treatment period. A comparison was also made after the first day of treatment.

Secondary efficacy variables were evening PEF, spirometry (FEV_1 and FVC), asthma symptoms, awakenings and use of rescue medication. In addition, the patient's assessment of his/her asthma condition was collected.

- **SAFETY**

Safety was assessed by collection and analysis of adverse events.

STATISTICAL METHODS

An Intention To Treat type of analysis was used. For the primary efficacy variable, morning PEF, averages were calculated for the last 10 days of the run-in period and for the whole treatment period. The change from run-in to the treatment period of these averages was analysed by an ANOVA model.

Secondary variables (except FEV_1 and FVC) were analysed in a manner similar to the primary variable.

FEV_1 and FVC were compared between treatments as the change from visit 2 (randomisation visit) to visit 3 (end of treatment).

The AEs were analysed by safety expertise at AstraZeneca R&D Lund, by means of descriptive statistics and qualitative analysis.

PATIENTS

Approximately 530 patients were to be enrolled (whereof 450 patients randomised) in order to reach 400 evaluable patients (200 per treatment arm).

	Symbicort	**Fluticasone**	**Total**
No. planned (rand)	225	225	450
No. randomised and treated	218	220	438
Males/Females	69/149	75/145	144/294
Mean age (range)	36.5 (18-75)	34.1 (17-66)	35.3 (17-75)
Baseline values			
Mean FEV_1 (%predicted)	2.36 L (77%)	2.43 L (77%)	2.40 L (77%)
Mean reversibility (%)	19.0	19.5	19.3
No. analysed for efficacy	218	220	438
No. analysed for safety	218	220	438
No. completed	215	213	428

SUMMARY

- EFFICACY RESULTS

Two weeks treatment with Symbicort Turbuhaler 80/4.5 μg b.i.d. was shown to increase the average morning PEF compared to two weeks treatment with fluticasone Diskus 250 μg b.i.d. The mean difference between the treatments was 10.5 L/min (95% confidence interval: 2.9-18.1).

	Symbicort 80/4.5 μg			fluticasone 250 μg			Symbicort - fluticasone		
Variable	run-in	treat.	change	run-in	treat.	change	mean	95% conf.lim.	P-value
PEF (L/min)									
-morning	329.8	367.4	36.7	351.3	376.8	26.2	10.5	2.9 - 18.1	0.0070
-evening	338.9	369.8	30.4	362.3	381.2	19.6	10.8	3.6 - 17.9	0.0033

Symbicort was shown to increase morning PEF compared to fluticasone already on the first day of treatment. The mean difference between the treatments the first day was 15.8 L/min (95% confidence interval: 7.4-24.3).

For the secondary efficacy variables, Symbicort was shown to increase average evening PEF and evening PEF the first day of treatment compared to fluticasone. No differences between the two treatments could be shown for the other secondary efficacy variables.

- SAFETY RESULTS

- The AEs had a similar distribution between the treatment groups regarding nature, frequency and intensity.

- One SAE was reported during treatment with fluticasone Diskus. Causal relationship to treatment was judged to be unlikely.
- Four randomised patients discontinued due to adverse events. No apparent treatment related differences were discernable.