AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide/Formoterol	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SD-039CR-0665		
VERSION NO.	Final		
STUDY CODE	SD-039-0665		
DATE	11 October, 2000		

FINAL

Symbicort Low Dose Once Daily In Mild To Moderate Asthmatic Patients

STUDY CENTRE(S)

Table 1 Coordinating Investigators

Table 1.

Finland	
Germany	
Mexico	
New Zealand	
Norway	
Poland	
Russia	
Sweden	

This was a multicentre study performed in eight countries, involving 60 clinical centres.

The countries are: Finland (5 centres), Germany (17 centres), Mexico (4 centres), New Zeeland (3 centres), Norway (6 centres), Poland (7 centres), Russia (5 centres), Sweden (13 centres).

Synopsis Document No. SD-039CR-0665 Study code SD-039-0665	(For national authority use only)

PUBLICATION (REFERENCE)

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	November 15, 1999	IIIA
- **DATE OF LAST PATIENT COMPLETED**	July 17, 2000	

OBJECTIVES

The primary objective was to compare the efficacy of Symbicort Turbuhaler 80/4.5 μg two inhalations given once daily in the evening with that of Pulmicort Turbuhaler 200 μg given once daily in the evening, and Symbicort Turbuhaler 80/4.5 μg given twice daily over a twelve week treatment period.

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

The primary variable was morning PEF. Secondary variables were spiromtry and diary card variables.

STUDY DESIGN

Double-blind, double-dummy, randomised, active-controlled, parallel group design.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Diagnosis Asthma.

Inclusion criteria: Male or female out-patients with asthma, 18 years and older, currently treated with a stable dose of 200-500 μg inhaled GCS for at least 30 days prior to visit 1. Patients should have a FEV_1 of 60-90% of predicted normal and show reversibility of FEV_1 ≥12% after inhalation of either 1 mg terbutaline sulphate or 0.4 mg of salbutamol. Signed informed consent had to be given by the patient.

Exclusion criteria: Respiratory infection within 4 weeks prior to visit 1. Other diseases and disorders that may interfere with study assessments, as judged by the investigator. Pregnant or lactating women. Known hypersensitivity to any of the study drugs or inhaled lactose. Smoking history ≥ 10 pack-years. Present use of β-blocker therapy (incl. eye-drops). Patient previously randomised into the study.

Criteria for allocation of patient number: The patient should show competence in using Mini-Wright® peak flow meter and be compliant in completing diary cards and assessments.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Symbicort® Turbuhaler® 80/4.5 μg, modified version, (budesonide/formoterol) 60 doses, Batch AF 26. Daily dose 80/4.5 μg two inhalations once daily.

Symbicort® Turbuhaler® 80/4.5 μg, modified version, (budesonide/formoterol) 60 doses, Batch AF 26. Daily dose 80/4.5 μg one inhalation twice daily.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Pulmicort® Turbuhaler®, original version (budesonide) 200 μg, 200 doses, Batch AA 1072. Daily dose 200 μg QD by inhalation.

Placebo Pulmicort® Turbuhaler® original version (Lactose) Batch AD 32.

Placebo Symbicort® Turbuhaler® modified version (Lactose) Batch AF 16, ZM 14.

Run-in

Pulmicort® Turbuhaler® 100 μg, 200 doses, Batch ZI 346. Daily dose 100 μg one inhalation once daily.

Patients were offered Bricanyl® Turbuhaler® 0.5 μg as rescue medication Batch AL 1138, AF 1119.

DURATION OF TREATMENT

12 weeks

MAIN VARIABLE(S):

- **EFFICACY**

The change in morning PEF was the primary variable over the 12 weeks treatment period.

Secondary variables were evening PEF, asthma symptoms, short-acting β_2-agonist use day and night, awakenings and FEV_1 and FVC.

- **SAFETY**

The safety variable was the reported 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 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 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 presicion. 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 Symbicort Turbuhaler QD and Pulmicort Turbuhaler QD.

PATIENTS

Approximately 550 patients were to be enrolled (and 450 randomized) to reach at least 390 evaluable patients.

	Symbicort QD 2x(80/4.5)μg	Symbicort b.i.d 80/4.5 μg	Pulmicort QD 200μg	Total
No. planned	183	183	183	549
No. randomized and treated	202	207	207	616
Males/Females	81/121	78/129	91/116	250/366
Mean age (range)	45.8 (18–80)	43.9 (19–80)	45.1 (18–78)	44.9 (18–80)
BMI (kg/m^2) range	26.6 (17–44)	26 (15–38)	25.9 (17–45)	26.2 (15–45)
Non-Smokers (n)	154	162	163	479
IGCS dose (μg)	363.4	370.5	367.5	367.2
Baseline values				
mPEF (L/min)	355.8	351.1	358.2	355.0
FEV_1 (% PN)	79.3	77.9	78.3	78.5
Reversibility (%)	23.5 (12-91)	23.4 (12-75)	23.2 (12-95)	23.3 (12-95)
Asthma symptoms night	0.4	0.5	0.5	0.5
Asthma symptoms day	0.7	0.8	0.7	0.7
Nighttime awakening (%)	15.8	14.6	17.9	16.1
Symptom free days (%)	37.8	36.1	38.1	37.4
Sum rescue use (range)	1.1 (0–8)	1.1(0–7)	1.2 (0–10)	1.1 (0–10)
No. analysed for efficacy	202	207	207	616
No. analysed for safety	202	207	207	616
No. completed	181	191	183	555

SUMMARY

- **EFFICACY RESULTS**

Table 2.

Variable	Symbicort QD vs Pulmicort QD	Symbicort b.i.d vs Pulmicort QD	Symbicort QD vs Symbicort b.i.d
mPEF-mean (P-value)	17.91 (p<0.001)	18.59 (p<0.001)	-0.68 (n.s.)
ePEF-mean (P-value)	11.27 (p=0.002)	19.95 (p<0.001)	-8.67 (p=0.015)
Change in β_2-agonist use	-0.12 (n.s)	-0.19 (p=0.047)	0.07 (n.s.)
Symptom free days (%)	6.63 (p=0.015)	6.94 (p=0.011)	-0.31 (n.s)
Asthma control days (%)	7.27 (p=0.007)	7.21 (p=0.007)	0.06 (n.s)

In terms of morning PEF, both Symbicort Turbuhaler treatments were shown to be more efficient than Pulmicort Turbuhaler. Both Symbicort Turbuhaler treatments showed better effect than Pulmicort Turbuhaler for evening PEF, rescue free days, symptom free days and asthma control days.

- **SAFETY RESULTS**

- 616 randomised patients experienced in total 315 AEs during randomised treatment.
- No deaths were reported in the study.
- Seven SAEs were reported during randomised treatment, all of which were considered unrelated to treatment.
- In total 36 DAEs were reported during the study; 26 discontinued due to DUS (Disease Under Study) deteriorated and 10 discontinued due to other AEs.