AstraZeneca

DRUG PRODUCT	Symbicort® Turbuhaler®	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide/formoterol	REFERRING TO PART	
DOCUMENT NO.	SD-039-CR-0348	OF THE DOSSIER	
VERSION NO.	01		
STUDY CODE	SD-039-0348		
DATE	6 April, 2000		

FINAL

Efficacy and safety of budesonide/formoterol Turbuhaler® (80/4.5 μg b.i.d.) in steroid-using asthmatic adults - "COMET"

STUDY CENTRE(S)

The study included 56 centres in the Czech Republic (10), Hungary (6), Norway (9), Poland (10), South Africa (5), Sweden (5) and the United Kingdom (11), of which 51 enrolled patients.

PUBLICATION (REFERENCE)

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	9 August, 1999	IIIA
- **DATE OF LAST PATIENT COMPLETED**	9 February, 2000	

OBJECTIVES

The primary objective was to compare the efficacy of budesonide/formoterol Turbuhaler 80/ 4.5 μg b.i.d. with budesonide Turbuhaler 200 μg b.i.d. over a 12-week treatment period. The primary efficacy variable was morning peak expiratory flow (PEF). Secondary variables were evening PEF, asthma symptoms, β_2-agonist use, and awakenings as recorded on diary cards. Lung function (forced expiratory volume in one second; FEV_1 and forced vital capacity; FVC) was measured at clinic visits.

The secondary objective was to study the safety of budesonide/formoterol Turbuhaler. Safety variable was adverse events.

STUDY DESIGN

This was a double-blind, double-dummy, randomised, active-controlled, multicentre study with a parallel-group design in asthmatic adults using inhaled glucocorticosteroids (iGCS).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Major inclusion criteria :

- Diagnosis of perennial asthma, with a minimum duration of 6 months prior to visit 1.
- Baseline FEV_1 value of 60-90% (≥60%, ≤90%) of predicted normal and a postbronchodilator reversibility in FEV_1 ≥12 % of prebronchodilator value.
- A fixed dose of iGCS for at least the last 30 days prior to visit 1. The daily dose had to be 200 - 500 μg iGCS of any brand.

Randomisation criteria :

- Patients were to demonstrate ability to use a Mini-Wright® PEF meter and to complete a diary card.
- Baseline diary data (morning PEF data) had to be recorded on at least 7 of the last 10 days of the run-in period.

Major exclusion criteria:

- Patients with unstable asthma, as defined by the use of oral, parenteral or rectal GCS within 30 days prior to visit 1.
- Seasonal asthma, prevalent at the time of the study.
- Women who were pregnant or planning a pregnancy during the study.
- Tobacco smokers or previous smokers, if they had a history of smoking ≥ 10 pack-years.
- Use of any β-blocker therapy (including eye-drops).

Criteria for discontinuation:

- Incorrect inclusion
- Patients that needed treatment with β-blockers, oral, parenteral or rectal GCSs
- Non-compliance
- Pregnancy

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide/formoterol Turbuhaler (new version) 80/4.5 μg b.i.d.

The following batches were used: Budesonide/formoterol: AF26, placebo budesonide/ formoterol: ZM14

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide Turbuhaler (current version) 200 μg b.i.d.

The following batches were used: Budesonide: ZF1014, AA1072, placebo budesonide: ZF30, AD32, AA31.

DURATION OF TREATMENT

The run-in period between visits 1 and 2 was about 2 weeks long, during which the patients were treated with budesonide Turbuhaler 100 μg b.i.d. (daily dose 200 μg).

The treatment period between visits 2 and 5 was 12 weeks (78-87 days) long with approximately 4 weeks between visits. The maximum number of treatment days allowed was 87. During the treatment period the patients received either: budesonide/formoterol Turbuhaler (60 doses), 80/4.5 μg, b.i.d. (daily dose: 160/9 μg) **or** budesonide Turbuhaler (200 doses), 200 μg, b.i.d. (daily dose: 400 μg). Terbutaline Turbuhaler 0.5 mg was provided as rescue medication.

MAIN VARIABLE(S):

- **EFFICACY**

Primary efficacy variable: morning PEF.

Secondary variables: evening PEF, asthma symptoms, short-acting β_2-agonist use day and night, and awakenings as recorded on diary cards, and lung function measurement (FEV_1 and FVC) assessed at clinic visits.

- **SAFETY**

The safety variable was incidence of adverse events (AEs).

STATISTICAL METHODS

For each variable analysed, data were reduced to one baseline value and one value on treatment. This was done by period means for diary card data and the last measurement obtained for clinic visit data. The basic analysis was therefore an analysis of variance of the value on treatment, using the baseline value as covariate and treatment and country and their interaction as factors. Treatment contrasts were weighted over countries according to precision.

PATIENTS

	BUD/FORM	**BUD**	**Total**
No. planned	130	130	260
No. randomized and treated	230	237	467
Males/Females	102/128	98/139	200/267
Mean age (range)	41.8 (18-77)	40.4 (18-78)	41.1 (18-78)
Baseline values:			
Mean iGCS dose (μg)	386	387	387
Mean FEV_1 (% of predicted)	81.9	81.4	81.7
Mean reversibility (%)	22.1	22.3	22.2
No. analysed for efficacy	230	237	467
No. analysed for safety	230	237	467
No. completed	215	215	430

SUMMARY

- EFFICACY RESULTS

Morning PEF increased by 16.5 L/min in the combination group (budesonide/formoterol Turbuhaler) compared with 7.3 L/min in the double-dose budesonide Turbuhaler group, and the difference of 9.2 L/min was statistically significant (p=0.002). Similar results were found in evening PEF, where the difference was 9.5 L/min (p<0.001), to the advantage of the combination group.

The frequency of days without the use of rescue medication was higher in the combination group (64.8%) than in the budesonide group (55.8%) (p<0.001).

Asthma symptom score and night-time awakenings were not statistically significant if inspecting the variables individually. However, for a symptom-free day, a day with no asthma symptoms or night-time awakenings, a difference was detected. To achieve, an asthma-controlled day, the patient should fulfil the criteria for symptom-free day and besides that, not have had any inhalations of rescue medication. By inspecting these variables an increase (8%) in the combination group was detected (p=0.002) compared with those receiving the monotherapy.

Treatment with the combination therapy increased the time to the first mild exacerbation (p=0.02), and decreased the relative risk for mild exacerbations by 26% (p=0.02) compared to those receiving the monotherapy.

- SAFETY RESULTS

The number and nature of adverse events were similar between the treatments. There were few serious adverse events (7 cases).