AstraZeneca

DRUG PRODUCT	Symbicort® Turbuhaler®	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide/formoterol	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SD-039-CR-0664B		
VERSION NO.	01		
STUDY CODE	SD-039-0664		
DATE	6 April, 2001		

FINAL

Safety of a combination of budesonide/formoterol in a single inhaler (Symbicort® Turbuhaler®) in steroid-using asthmatic adults - "COMSAFE-extension"

MEDICAL ADVISER

C. Hultquist, AstraZeneca R&D Lund, SE-221 87 Lund, Sweden.

STUDY CENTRE(S)

Twenty-nine centres from Sweden participated in this study.

PUBLICATION (REFERENCE)

Not applicable.

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT RANDOMIZED**	October 8, 1999	Phase III
- **DATE OF LAST PATIENT COMPLETED**	December 20, 2000	

OBJECTIVES

The primary objective of this study was to compare the safety of the combination of budesonide/formoterol in a single inhaler (Symbicort Turbuhaler®) 2 x 160/4.5 μg b.i.d. with that of budesonide Turbuhaler 2 x 200 μg b.i.d. + formoterol Turbuhaler 2 x 4.5 μg b.i.d. (BUD+FORM) via two separate inhalers over a 12-month treatment period. The secondary objective was to compare efficacy.

STUDY DESIGN

This was a 12-month open, randomized, active-controlled, parallel-group study in adult asthmatics using inhaled glucocorticosteroids (GCS) and either long- or short-acting β_2-adrenergic agonists on a daily basis. The study was initially a 6-month study with participating patients from Denmark, Finland, Norway and Sweden. The results from this 6-month period (Part A) have been reported previously (SD-039-CR-0664). The Swedish centres were offered to participate in another 6-month treatment period (Part B). In the

present report, only the results for patients enrolled by clinic centres participating in both Part A and Part B are presented.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Main inclusion criteria - Visit 1:

The main inclusion criteria were as follows:
1. Diagnosis of perennial asthma, with a minimum duration of 6 months.
2. FEV_1 ≥50% of predicted normal.
3. Use of 400 - 1200 μg inhaled GCS of any brand. The dose has to be fixed for at least 30 days prior to Visit 1.
4. Daily use of any long-acting β_2-adrenergic agonist, or daily (≥1 inhalation(s)/day) use of rescue medication (short-acting β_2-agonist).

Main exclusion criteria - Visit 1:

The main exclusion criteria were as follows:
1. Use of oral, parenteral or rectal GCS, leukotriene antagonists, inhaled sodium cromoglycate, inhaled nedocromil sodium, oral β_2-agonists, xanthines, or inhaled anticholinergics within 30 days prior to Visit 1.
2. Respiratory infection, judged by the investigator as affecting the asthma, within 30 days prior to Visit 1.
3. Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the result of the study, or the patient's ability to participate in the study.
4. Tobacco smoking, past or present, if there is a smoking history of ≥ 10 pack-years (i.e. the equivalent of one pack of 20 cigarettes/day for ten years).

Main discontinuation criteria

The main discontinuation criteria were as follows:
1. Incorrect inclusion.
2. Use of >2 courses of oral steroids during either Part A or Part B.
3. Need for parenteral, rectal or inhaled GCS (other than study medication).
4. Pregnancy.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide/formoterol Turbuhaler (Symbicort® Turbuhaler®), batch AF 19, 2 x 160/4.5 μg b.i.d., inhalation.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide Turbuhaler (Pulmicort® Turbuhaler®), batch AC 1099, 2 x 200 μg b.i.d. and formoterol Turbuhaler (Oxis® Turbuhaler®), batch AD 270, 2 x 4.5 μg b.i.d., inhalation.

DURATION OF TREATMENT

12 months.

MAIN VARIABLE(S):

- **SAFETY**

Safety variables included adverse events (AEs), pulse and blood pressure, ECG, urinalysis, clinical chemistry and hematology.

- **EFFICACY**

The efficacy variables included lung function measurements (FEV_1 and FVC), health-related quality of life (HRQL; assessed by use of the Mini Asthma Quality of Life Questionnaire; MiniAQLQ), symptom-based measure of asthma control (assessed by use of the Asthma Control Questionnaire; ACQ), and asthma-related health care resource utilization (the latter parameter will be reported in a separate health economics report).

In addition, at Visit 5 morning serum cortisol (S-cortisol) was assessed.

STATISTICAL METHODS

The safety variables were analyzed by means of descriptive statistics and qualitative analysis by safety expertise. The efficacy analysis was an intention-to-treat analysis where FEV_1 and FVC were analyzed as the change from baseline (values collected at Visit 1) to the average of the values at Visit 5 and 6 in a multiplicative ANOVA. MiniAQLQ and ACQ were analyzed in a similar way but with an additive ANOVA. Health care resource utilization was summarized for each treatment group. The S-cortisol values were analyzed with a multiplicative ANOVA model.

PATIENTS

Randomization was skewed (2:1) and, initially, the aim was to have 300 fully evaluable patients in the group treated with Symbicort and 150 patients in the group treated with budesonide and formoterol in two separate inhalers for 6 months. When the study period was extended, all Swedish centres were offered to participate in another 6-month treatment period.

	Symbicort	**BUD+FORM**	**Total**
Randomized and treated	218	103	321
Men/women	97/121	50/53	147/174
Mean age (range)	44.0 (18-78)	43.2 (19-78)	43.7 (18-78)
Analyzed for efficacy	218	103	321
Analyzed for safety	218	103	321
Completers (Part A + Part B)	198	83	281

SUMMARY

- SAFETY RESULTS

- There were no clinically important differences between the treatment groups regarding the proportion, nature or intensity of the AEs.
- 14 patients reported serious adverse events (SAEs); 8 (4%) in the Symbicort group and 6 (6%) in the BUD+FORM group. All SAEs were considered to be unrelated to study treatment, except one (unspecified eye symptoms/headache, BUD+FORM) which was considered to be possibly related to the investigational product by the investigator.
- 15 (5%) randomized patients discontinued due to AEs. The frequency of discontinuations due to disease under study (DUS) deterioration was slightly higher in the BUD+FORM group than in the Symbicort group, but the frequency of discontinuations due to other AEs was similar between the treatment groups.
- No clinically important differences between the treatment groups, or changes over time within the treatment groups, were identified for laboratory measurements (including morning S-cortisol), vital signs or ECG.

- EFFICACY RESULTS

There was no evidence of a difference between treatment with Symbicort and with BUD+FORM with regard to lung function (i.e. FEV_1 or FVC), HRQL (MiniAQLQ) or asthma control (ACQ).