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-0664		
VERSION NO.	01		
STUDY CODE	SD-039-0664		
DATE	20 August, 2000		

FINAL

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

STUDY CENTRE(S)

Sixty-one centres from four countries participated in this multicentre study: Denmark (8 centres), Finland (15), Norway (6), and Sweden (32).

PUBLICATION (REFERENCE)

Not applicable.

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT RANDOMIZED	September 8, 1999	Therapeutic use
- DATE OF LAST PATIENT COMPLETED	June 20, 2000	

OBJECTIVES

The primary objective of this study was to compare the safety of the combination budesonide/formoterol in a single inhaler (Symbicort Turbuhaler®) 2 x 160/4.5 μg b.i.d. with the safety of the combination of budesonide Turbuhaler 2 x 200 μg b.i.d. + formoterol Turbuhaler 2 x 4.5 μg b.i.d. (BUD+FORM) in two separate inhalers over a 6-month treatment period. The secondary objective was to compare efficacy.

STUDY DESIGN

This was a 6-month open, randomized, active-controlled, parallel-group study in adult asthmatics using inhaled steroids and either long-acting β_2-agonists or short-acting β_2-agonists on a daily basis.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Main inclusion criteria - Visit 1:

The major 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 glucocorticosteroid (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-agonist, or daily (≥1 inhalation(s)/day) use of rescue medication (short-acting β_2-agonist).

Main exclusion criteria - Visit 1:

The major 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. Severe cardiovascular disorder, such as ischaemic heart disease, tachyarrhythmias or severe heart failure, as judged by the investigator.
4. 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.
5. 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 major discontinuation criteria were as follows:
1. Incorrect inclusion.
2. Use of >2 courses of oral steroids.
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

6 months (minimum 182 and maximum 196 days of treatment).

MAIN VARIABLE(S):

- **EFFICACY**

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

- **SAFETY**

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

STATISTICAL METHODS

The safety variables were analysed 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 analysed as the change from baseline (values collected at Visit 1) to the average of the values at Visit 3 and 4 in a multiplicative ANOVA. MiniAQLQ and ACQ were analysed in a similar way but with an additive ANOVA. Health care resource utilization was summarized for each treatment group.

PATIENTS

Randomization was skewed (2:1) and 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. To reach this aim a total of 586 patients were randomized.

	Symbicort	**BUD+FORM**	**Total**
Planned	360	180	540
Randomized and treated	390	196	586
Men/women	168/222	89/107	257/329
Mean age (range)	45.2 (18-81)	44.4 (18-78)	45.0 (18-81)
Analysed for efficacy	390	196	586
Analysed for safety	389	196	585
Completers	364	175	539

SUMMARY

- **EFFICACY RESULTS**

There was no evidence for a difference between treatment with Symbicort and with budesonide and formoterol in two separate inhalers, with regard to lung function (i.e. FEV_1 or FVC), QoL (MiniAQLQ), or asthma control (ACQ).

- **SAFETY RESULTS**

Individual patient changes and individual abnormalities, including changes over time, for laboratory measurements, vital signs and ECG parameters showed no clinically important differences between the treatment groups. The AEs reported during the study showed a similar distribution between the treatment groups. 18 patients with SAEs were reported; 13 (3.3%) in the Symbicort group and 5 (2.6%) in the BUD+FORM group. All SAEs were considered to be unrelated to study treatment, except one (unspecified eye symptoms, BUD+FORM) which was considered to be possibly related to the investigational product by the investigator. 32 randomized patients discontinued due to AEs and these discontinuations had a similar distribution between the treatment groups.