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-0349		
VERSION NO.	01		
STUDY CODE	SD-039-0349		
DATE	11 November, 1999		

FINAL

Efficacy and safety of a fixed combination of budesonide/formoterol Turbuhaler® in inhaled steroid-using asthmatic adults.

STUDY CENTRES

The study included 63 centres, in Finland (7), Germany (12), Ireland (6), Norway (12), Spain (11) and Sweden (15) of which 59 enrolled patients.

PUBLICATION (REFERENCE)

STUDY PERIOD

- **DATE OF FIRST PATIENT ENROLLED**
  15 October, 1998
- **DATE OF LAST PATIENT COMPLETE**
  29 June, 1999

PHASE OF DEVELOPMENT

IIIA

OBJECTIVES

The primary objective was to compare the efficacy of the fixed combination budesonide/formoterol Turbuhaler with that of budesonide Turbuhaler over a 12-week treatment period.

Secondary objectives were: 1) To compare the efficacy of the fixed combination budesonide/formoterol Turbuhaler with the free combination of budesonide Turbuhaler and formoterol Turbuhaler, and 2) to determine the safety of budesonide/formoterol Turbuhaler and the other treatments.

STUDY DESIGN

This was a double-blind, double-dummy, randomised, active-controlled, multicentre study with a parallel-group design in asthmatic adults using inhaled GCS. Patients using a

constant daily dose of ≥ 500 μg of inhaled GCSs were recruited for the study. After a two- to three-week run-in period during which the patients inhaled their regular inhaled GCS dose, patients were randomised to a 12-week double-blind treatment period with the fixed combination of budesonide/formoterol 160/4.5 μg x 2 inhalations b.i.d. via Turbuhaler (M3), budesonide 200 μg x 2 inhalations b.i.d. via Turbuhaler (M2) or to the free combination budesonide 200 μg + formoterol 4.5 μg x 2 inhalations b.i.d. via Turbuhaler (M2).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Major inclusion criteria:

- An initial diagnosis of asthma
- Baseline FEV_1 of predicted normal value of 50-90% and reversibility in FEV_1 ≥ 15 % of basal value
- A fixed dose of inhaled GCS for at least the last 30 days prior to visit 1. The daily inhaled dose had to be: ≥ 800 μg inhaled budesonide Turbuhaler, ≥ 500 μg fluticasone propionate, ≥ 1000 μg BDP any formulation, or budesonide pMDI.

Randomisation criteria:

- Patients were to demonstrate ability to use a peak flow meter and to complete a daily diary card
- Morning PEF data 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
- Females 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
- Pregnancy

TEST AND COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

At visit 2, each patient received two sets (delivered in two boxes) with three inhalers in each set and was instructed to inhale according to the following scheme: the fixed combination group, inhaler No. 1, budesonide/formoterol 2 x 160/4.5 μg b.i.d. and inhaler No. 2, 2 x placebo b.i.d, and inhaler No. 3, 2 x placebo b.i.d. The budesonide group, inhaler No. 1, 2 x placebo b.i.d., inhaler No. 2, budesonide 2 x 200 μg b.i.d., and inhaler No. 3, 2 x placebo b.i.d. The free combination group, inhaler No. 1, 2 x placebo b.i.d, inhaler No. 2, budesonide 2 x 200 μg b.i.d., and inhaler No. 3, formoterol 2 x 4.5 μg b.i.d.

The following batches were used: Bud/form: ZG14, ZG15. Placebo bud/form: ZH13. Bud YG923, ZF1014, placebo bud: ZD29, ZF30. Form ZB11, ZI242, ZL17, placebo form: ZC14, ZF15.

DURATION OF TREATMENT

The run-in period between visit 1 and 2 was about 2-3 weeks long. The treatment period between visit 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 days.

MAIN VARIABLE(S):

- **EFFICACY**

Primary variable: morning PEF.

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

- **SAFETY**

Adverse events (AE) and laboratory measurements.

STATISTICAL METHODS

The primary analysis was an intention-to-treat analysis, including all randomised patients who had received at least one dose of study medication. The primary efficacy variable was the change from baseline to end of treatment in morning PEF. Averages were calculated for morning PEF for the last 10 days of the run-in period and for the whole of the treatment period. The change from run-in to the treatment period of these averages was analysed by an ANOVA model with factors treatment and country and with the run-in average as covariate.

PATIENTS

	BUD/FORM	**BUD+FORM**	**BUD**	**Total**
No. planned	100	100	100	300
No. randomised and treated	123	115	124	362
Males/Females	65/58	58/57	62/62	185/177
Mean age (years)	46.7	44.7	48.5	46.7
Baseline values:				
Inhaled GCS dose (μg)	971.1	973.5	936.3	960.3
FEV1 (% of predicted)	73.6	74.7	73.1	73.8
Reversibility (%)	21.5	22.2	23.8	22.5
No. analysed for efficacy	123	115	124	362
No. analysed for safety	123	115	124	362
No. completed	103	98	108	309

SUMMARY - CONCLUSIONS

- **EFFICACY RESULTS**

Morning PEF in the fixed combination group increased by 36 L/min from baseline whereas the mono therapy group remained on the run-in level. The difference in morning PEF between the fixed combination and the mono therapy group was statistically significant ($p<0.001$). The free combination of budesonide and formoterol increased morning PEF by 32 L/min compared to budesonide alone ($p<0.001$). There was no statistically significant difference in efficacy between the fixed combination and the free combination of budesonide and formoterol. The secondary variables (evening PEF, symptom scores, rescue medication use, and FEV_1) were statistically significantly improved by the combination therapies compared to mono therapy alone.

- **SAFETY RESULTS**

The number, nature and intensity of AEs were similar between the treatments and the laboratory measurements did not suggest any adverse drug effects. There were 5 serious adverse events of which none was considered causally related to treatment.