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-0353		
VERSION NO.	01		
STUDY CODE	SD-039-0353		
DATE	30 November, 1999		

FINAL

Efficacy and safety of budesonide/formoterol Turbuhaler® in a fixed combination in steroid-using asthmatic children - **COMIC** .

STUDY CENTRES

The study included 48 centres, of which 43 enrolled patients; Hungary (6), the Czech Republic (7), the United Kingdom (11), Spain (7), Belgium (4), Israel (4) and South Africa (4).

PUBLICATION (REFERENCE)

STUDY PERIOD

- **DATE OF FIRST PATIENT ENROLLED, 3 November, 1998**
- **DATE OF LAST PATIENT COMPLETED, 24 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.

The secondary objective was to determine the safety of the treatments. Safety was assessed through recording of adverse events.

STUDY DESIGN

This was a double-blind, double-dummy, randomised, active-controlled, parallel-group, multi-centre study in asthmatic children using inhaled GCSs. After an open 2- to 4-week run-in period on budesonide via Turbuhaler, 2 x 100 μg b.i.d., the patients were stratified into two age groups (4-11 years or 12-17 years) and entered a 12-week treatment period

with either 2 x 80/4.5 μg b.i.d. budesonide/formoterol Turbuhaler (delivered dose) or 2 x 100 μg b.i.d. budesonide Turbuhaler (metered dose).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Major inclusion criteria:

- An initial diagnosis of asthma
- Baseline FEV_1 40 - 90% of predicted normal value, reversibility in $FEV_1 \geq 15$ % of basal value
- A fixed dose of inhaled GCS at least 6 weeks prior to visit 1. The daily dose had to be: ≥ 400 μg budesonide Turbuhaler, ≥ 600 μg budesonide pMDI, ≥ 375 μg fluticasone propionate in any device, ≥ 600 μg beclomethasone dipropionate in any device

Randomisation criteria;

- Baseline FEV_1 ≤100% of the predicted normal value, reversibility in $FEV_1 \geq 12\%$ of basal value
- 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 GCSs within 30 days prior to visit 1
- Respiratory infection affecting the asthma within 4 weeks prior to visit 1.

Criteria for discontinuation:

- Incorrect inclusion
- Need for treatment with 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 two 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 80/4.5 μg b.i.d. and inhaler No. 2, 2 x placebo b.i.d. The budesonide group, inhaler No. 1, 2 x placebo b.i.d., inhaler No. 2, budesonide 2 x 100 μg b.i.d.

The following batches were used: Budesonide/formoterol: ZG22, ZG23. Placebo budesonide/formoterol: ZH13. Budesonide YG315, ZB326, ZE334. Placebo budesonide: YI27, ZF30.

DURATION OF TREATMENT

The run-in period between visit 1 and 2 was about 2-4 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 efficacy variable: morning PEF.

Secondary variables: evening PEF, asthma symptoms, β_2-agonist use day and night, awakenings as recorded in diary cards, lung function measurements (FEV_1, FVC) at clinic visits, and in a subpopulation, repeated FEV_1 measurements over 12 hours.

- **SAFETY**

Adverse events (AEs).

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 the change in morning PEF from baseline to end of treatment. 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 in these averages was analysed using an ANOVA model with factors treatment, country, ageclass, and with the run-in average as covariate.

PATIENTS

	Bud/form	**Bud**	**Total**
No. planned	100	100	200
No. randomised and treated	148	138	286
Boys/Girls	90/58	87/51	177/109
Mean age (years)	10.6	10.9	10.8
Baseline values			
Inhaled GCS dose (μg)	547.3	548.3	547.8
FEV1 (% of predicted)	73.7	75.6	74.6
Reversibility (%)	21.4	20.9	21.2
No. analysed for efficacy	148	138	286
No. analysed for safety	148	138	286
No. completed	139	129	268

SUMMARY

- **EFFICACY RESULTS**

The primary variable, morning PEF, increased by 23 L/min in the fixed combination group and 11 L/min in the budesonide group. The difference between the groups was statistically significant ($p<0.001$). Statistically significant difference ($p<0.001$) was also demonstrated for evening PEF where the fixed combination increased by 20 L/min whereas the budesonide group only increased by 8 L/min. In addition, FEV_1 measurements and repeated

FEV_1 measurements over 12 hours, were improved on the 5 % significance level by the fixed combination compared to budesonide alone.

- **SAFETY RESULTS**

There were no statistically significant differences in the adverse event profile between Symbicort Turbuhaler and budesonide. All serious adverse events were either asthma exacerbations or isolated incidents, and all were considered unrelated to the study drug. The number of discontinuations due to adverse events was similar between the treatment groups. The incidence of undesirable class effects for β2-agonists and inhaled steroids was low.