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CLINICAL STUDY REPORT

DRUG SUBSTANCE	Budesonide
DOCUMENT NO.	
VERSION NO.	01
STUDY CODE	SD-004-0377
DATE	31 May , 2000

FINAL

Once daily administration of 200 μg budesonide Turbuhaler® and 200 μg fluticasone propionate via Diskus® inhaler in stable asthmatics

STUDY PERIOD:	June 12, 1998 through November 28, 1999
PHASE OF DEVELOPMENT:	IV
STUDY DESIGN:	Double-blind, randomized, reference-controlled, parallel group
DIAGNOSIS:	Asthma
TEST DRUG AND DOSAGE:	Budesonide Turbuhaler 200 μg once daily
COMPARATOR DRUG AND DOSAGE:	Fluticasone propionate 200 μg once daily via the Diskus
DURATION OF TREATMENT:	12 weeks

The study was conducted in accordance with the principles of Good Clinical Practice.

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DRUG PRODUCT DRUG SUBSTANCE(S) Budesonide DOCUMENT NO. VERSION NO. 01 STUDY CODE SD-004-0377 DATE 31 May , 2000		**Synopsis** REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)

FINAL

Once daily administration of 200 μg budesonide Turbuhaler® and 200 μg fluticasone propionate via Diskus® inhaler in stable asthmatics

INVESTIGATOR

STUDY CENTRE(S)

This was a multicentre study performed in seven countries, involving 44 clinical centers. The countries were: Portugal (4 centers), Spain (12 centers), France (10 centers), the Philippines (10 centers), Malaysia (2 centers), Thailand (2 centers) and Indonesia (4 centers). Belgium was to be involved but cancelled participation due to difficulties in finding suitable patients.

PUBLICATION (REFERENCE)

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Synopsis Document No. Study code SD-004-0377	(For national authority use only)

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT ENROLLED	June 12, 1998	IV
- DATE OF LAST PATIENT COMPLETED	November 28, 1999	

OBJECTIVES

The objective of this study was to compare the efficacy of 200 μg budesonide Turbuhaler once daily with 200 μg fluticasone propionate once daily from the Diskus inhaler. Primary efficacy variable was time to loss of asthma control.

The study also examined the cost-effectiveness of the two therapies.

STUDY DESIGN

Double-blind, randomized, reference-controlled, parallel group.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Diagnosis: Asthma.

Inclusion criteria: Male or female out-patient, with asthma, aged 18-65 years currently treated, for at least the last 3 months prior to Visit 1, with 200-500 μg bid, via pMDI, beclomethasone dipropionate, flunisolide, or budesonide. Patients should have an FEV_1 or PEF of ≥85 % of predicted normal before bronchodilator and asthma should be well controlled as judged by the investigator. Signed informed consent should be given by the patient.

Exclusion criteria: Seasonal asthma, clinical obstructive pulmonary disease or pulmonary dysfunction other than asthma. Temporary change in dose of inhaled steroid, or use of oral steroid, over the last 8 weeks prior to Visit 1. Previous use of Diskus or Diskhaler. Other disease that may interfere with the study assessments, as judged by the investigator. Patient hospitalized during the past 30 days due to asthma. Use of antibiotics during the past 30 days due to airway disease.

Criteria on allocation of patient number: The patient should have less than 5 occasions of bronchodilator medication over the last five-day period prior to randomization. The patient should be competent, as judged by the physician, in using Turbuhaler and the Diskus inhaler according to the package insert and compliant in following instructions i.e. completion of diary cards and assessments.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide Turbuhaler 100 μg/dose, 200 doses. Batch: ZB 326. Daily dose: 200 μg q.d.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Fluticasone propionate 100 μg/dose, 60 doses. Batches: WP2NMG, WP2PXW, WP2NGA, WP2L57, WP2F2K, WP2KFC, WP2JJ1, WP2FTD, WP2F02. Daily dose: 200 μg q.d.

Placebo Turbuhaler. 200 doses. Batches: ZL 31, ZA 28. Daily use: q.d.

Placebo Diskus (Accuhaler) inhaler. 60 doses. Batches: DAC 6, DZA. 4. Daily use: q.d.

DURATION OF TREATMENT

12 weeks.

MAIN VARIABLE(S):

- **EFFICACY**

Time to loss of asthma control was the primary variable. Loss of asthma control was considered to occur on the first occasion when the patient experienced two poorly controlled days within a five-day period. Time to loss of asthma control was established by analysing the diary card variables.

Control was identified from a global assessment of PEF, asthma symptoms, need of rescue medication and questions relating to patient behavior.

- **SAFETY**

In this study, adverse events due to deterioration of asthma were reported in the form “Discontinuation due to adverse event”. Other adverse events were not collected. Serious adverse events were reported.

- **HEALTH ECONOMICS**

The cost-effectiveness of the two therpies was investigted.

STATISTICAL METHODS

The primary efficacy variable was analyzed using survival analysis with Kaplan-Meier estimates. These data were analyzed using a Log-rank test.

PATIENTS

At least 550 patients were planned to be randomized in this multicentre study.

Table 2. Demography and baseline data

	Budesonide	**Fluticasone propionate**	**Total**
No. Patients, planned (n)	275	275	550
No. Patients, randomized and treated (n)	273	276	549
Males/Females (n)	81 / 192	87 / 189	168 / 381
Age (years), mean	35.5	35.9	35.7
Race (n): - Caucasian	72	77	149
- Black	2	2	4
- Oriental	199	197	396
Baseline values:			
Duration of asthma (years), mean	13.6	12.7	13.2
Smokers (n), ever	48	37	85
PEF - morning (L/min), mean	386.5	375.8	380.0
Rescue medication - nighttime, mean occasions	0.08	0.08	0.08
Rescue medication - daytime, mean occasions	0.08	0.12	0.10
Asthma symptoms - nighttime, mean score	0.20	0.17	0.19
Asthma symptoms - daytime, mean score	0.19	0.22	0.21
Awakening at night due to asthma, mean number	0.09	0.06	0.07
No. analyzed for efficacy	269	273	542
No. analyzed for safety	273	279	549
No. completed	244	245	489

SUMMARY - CONCLUSION(S)

- EFFICACY RESULTS

The statistical analysis of the primary variable “time to loss of asthma control” showed no statistical difference between the two treatments groups (p=0.091). Patients who experienced loss of asthma control were fewer than anticipated in the study protocol, i.e. the number of patients who did experience loss of asthma control was less than 50% of the randomized patients in both treatment groups. Only 23 (<5%) out of 549 patients left the study due to deterioration of asthma that necessitated additional asthma treatment. For the clinical measurements (spirometry and PEF) it was not possible to demonstrate any significant difference between the two treatment groups.

- SAFETY RESULTS

Based on the limited amount of safety data collected (registration of SAEs/DAEs), no new safety signals were identified.

- **HEALTH ECONOMICS**

The health economics analysis of this study showed no difference in effectiveness between the drugs, and concluded on a cost-minimisation basis that budesonide should be preferred to fluticasone propionate at equal doses both in a health care perspective and a societal perspective.

DATE OF THE REPORT

May 31, 2000