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CLINICAL STUDY REPORT

DRUG SUBSTANCE	Budesonide Turbuhaler
DOCUMENT NO.	CR-004-0378
VERSION NO.	1
STUDY CODE	SD-004-0378
DATE	10 03, 2003

FINAL

The effects of budesonide (Pulmicort®) Turbuhaler® 400 μg once daily or montelukast sodium (Singulair®) 10 mg once daily on inflammation in mild steroid-free asthmatics following Low Dose Allergen Challenge

STUDY PERIOD:	March 2, 1999 through April 13, 2001
PHASE OF DEVELOPMENT:	II
STUDY DESIGN:	Double-blind, randomized, double-dummy, placebo-controlled, paralell-group design
DIAGNOSIS:	Asthma
TEST DRUG AND DOSAGE:	Pulmicort Turbuhaler 400 μg OD
COMPARATOR DRUG AND DOSAGE:	Singulair tablet 10 mg OD
DURATION OF TREATMENT:	8 weeks

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

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DRUG PRODUCT DRUG SUBSTANCE(S) Budesonide Turbuhaler DOCUMENT NO. CR-004-0378 VERSION NO. 1 STUDY CODE SD-004-0378 DATE 10 03, 2003	**Synopsis** REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)

FINAL

The effects of budesonide (Pulmicort®) Turbuhaler® 400 μg once daily or montelukast sodium (Singulair®) 10 mg once daily on inflammation in mild steroid-free asthmatics following Low Dose Allergen Challenge

INVESTIGATOR

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STUDY CENTRE(S)

This is a multicentre study performed in Canada, involving two centres, McMaster University and Laval University.

PUBLICATION (REFERENCE)

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT ENROLLED	March 1999	II
- DATE OF LAST PATIENT COMPLETED	April 2001	

OBJECTIVES

The objective was to compare the effects of 8 weeks treatment with budesonide Turbuhaler 400μg or montelukast 10 mg, both given once daily in the evening, on airway inflammation in steroid-free asthmatics

The primary variable was eosinophils in sputum after Low Dose Allergen Challenge

Secondary variables were exhaled nitric oxide (ENO), bronchial hyperresponsiveness (BHR) measured as PC_{20} metacholine, and differential white blood cell (WBC) count in peripheral blood and sputum. Eosinophils and Eosinophilic Cationic Protein (ECP) in bronchial biopsies were also to be secondary variable. Furthermore, the sputum samples, biopsies and

the peripheral blood were investigated exploratively for levels of soluble and cellular markers whose value as markers for airway inflammation not yet established.

Other secondary variables were lung function measured at clinic visits (forced expiratory volume in one second, FEV_1) and peak expiratory flow (PEF) measured daily by the patient, as well as symptom scores and use of rescue medication.

STUDY DESIGN

The study was of a double-blind, randomized, placebo-controlled, double-dummy paralell-group design.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Diagnosis asthma

Inclusion criteria: Male or female out-patients with asthma acc. to ATS, aged 18 - 60 years, not treated with inhaled GCS for the last 6 months prior to visit 1. Patients should have PC_{20} (methacholine) less than 16 mg/mL and were atopic asthmatis showing a late response following the screening og high dose allergen challenge. Patients were non smoking one month prior to visit 1 and non-smoker at present with a history of less than 10 pack-years ever. Signed inform consent was given by the patient.

Exclusion criteria: Respiratory infection and other diseases that may interfere with study assessments, as judged by the investigator. No asthma exacerbation within 30 days prior to visit 1. Patients having a FEV_1 less than 70% of predicted normal. Pregnant or lactating women. Previous treatment with leukotriene modifiers. Known intolerance to any of the study drugs or inhaled lactose.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide (Pulmicort®)Turbuhaler® (powder for inhalation) delivering 200 μg/dose, 200 doses. Batch YG 923, YK 948, AA 1072, AI 1144. Daily dose 400 μg once daily

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Tablet Montelukast sodium (Singulair®) 10 mg, 64 tablets. Batch CO 13510/1, CO 15170/1, EO 01510/1, EO 02740/2, EO 02740/2, EO 04660/1, EO 08260/1, EO 09710/1, EO 12380/1, FO 04500/1, FO 08030/1, FO 11190/1. Daily dose 10 mg, one tablet once daily.

Placebo (lactose) Pulmicort Turbuhaler, 200 doses. Lactose. Batch ZD 29, ZF 30, AD 32, AI 33. Once daily.

Tablet Placebo montelukast Singulair 64 tablets, Lactose. Batch DAA 4/1, DAL 5/1. Daily dose once daily.

DURATION OF TREATMENT

Eight weeks

MAIN VARIABLE(S):

- **EFFICACY**

The change in sputum eosinophils following low-dose allergen challenge was the primary variable.

Secondary variables were the exhaled nitric oxide (ENO), bronchial hyperresponsiveness (BHR) measured as PC_{20} methacholine, and differential white blood cell count (WBC) in peripheral blood and sputum. Eosiniphils and eosinophilic cationic protein (ECP) in bronchial biopsies. Furthermore, in sputum samples, biopsies and the perpheral blood were investigated exploratively for levels of soluble and cellular markers.

Other secondary variables were lung function (FEV_1) and peak expiratory flow (PEF) as well as symptoms scores and use of rescue medication.

- **SAFETY**

The safety is this study was the reporting of Serious Adverse Events (SAE) and Discontinuation due to adverse event.

STATISTICAL METHODS

An intention To Treat type analysis was used with all available data. Missing data were replaced using the Last Value Extended (LVE) principle, within the run-in period and within the treatment period separately. No values were extended between periods. Any variable measured both before and after Low Dose Allergen Challenge (LDAC) was considered as two separate variables and LVE was not used to replace a missing value after LDAC with one taken before LDAC, and conversely, missing values before LDAC were not replaced by values after LDAC. The same type of analysis was used for the majority of variables. An ANOVA model with treatment and centre as factors, and with the baseline value as covariate was used for all variables. A multiplicative ANOVA model, i.e. the endpoint and the covariate were log-transformed before analysis, was used for all variables with the exception of lung function variables (FEV_1, FVC, and VC) and diary card variables (PEF, rescue use and symptoms) where an additive model was used. All hypothesis testing was done using two-sided alternative hypothesis. P-value less than or equal to 5% were considered statistically significant.

PATIENTS

	Budesonide	Montelukast	Placebo	**Total**
No. planned	15	15	15	45
No. randomized and treated	14	12	13	39
Males/Females	6/8	2/10	6/7	14/25
Mean age	25	25	28	26
Baseline values				
BMI (KG/M^2)	24	25	26	25
FEV_1	3.47	3.2	3.36	3.35
PC_{20} (mg/mL)	1.70	2.12	1.66	1.80
Asthma control days	60	54	62	59
No. analysed for efficacy	14	12	13	39
No. analysed for safety	14	12	13	39
No. completed	14	11	13	38

SUMMARY - CONCLUSION(S)

The study failed to show any statistical significant effect of budesonide and montelukast in comparison with placebo on sputum eosinophils after low dose allergen challenge (LDAC).

The original protocol stipulated the study population should have increased levels of sputum eosinophils, and this was ensured by an inclusion criteria reguiring sputum eosinophil levels of more than 3% at both visit 1 and 2. In reality these patients could not be found and this criteria was replaced with one that reguired a response to high dose allergen challenge. However, the inclusion criteria did not stipulate sensitivity to LDAC nor elevated eosinophil levels in response to LDAC. Furthermore the criteria of PC_{20} was changed from less than 8mg/mL to less than 16mg/mL. With these changes, the study population became less strict with respect to evaluation of the primary variable - change in sputum eosinophil levels in response to LDAC.

The response to LDAC decreased over time in all treatment groups, making the basis for conclusions regarding differences in treatment effects hazardous. Furthermore, since the study included many variables of explorative nature, the presence of a statistically significant effect in one variable could not be excluded as a finding of change if it was not substantiated by similar findings in associated variables.

In conclusion, the study failed to show any statistical significant effect of budesonide and montelukast in comparison with placebo on sputum eosinophils after low dose allergen challenge.

- **SAFETY RESULTS**

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