AstraZeneca

DRUG PRODUCT DRUG SUBSTANCE(S) Budesonide DOCUMENT NO. SD-004CR-0216 VERSION NO. Final STUDY CODE SD-004-0216 DATE 11 December, 2000		**Synopsis** REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)

FINAL

Oxis Turbuhaler® (formoterol), Accolate® (zafirlukast) or placebo as add on treatment to Pulmicort Turbuhaler® (budesonide) in asthmatic patients on inhaled steroids

INVESTIGATOR

STUDY CENTRE(S)

This is a multicentre study performed in six countries, involving 49 clinical centres. The countries are: Argentina (8 centres), Austria (6 centres), Finland (8 centres), Czech Republic (11 centres), Ireland (9 centres) and Poland (7 centres)

PUBLICATION (REFERENCE)

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	April 1998	IV
- **DATE OF LAST PATIENT COMPLETED**	January 2000	

ASTRAZENECA R&D LUND, S-221 87 LUND SWEDEN, TEL +46 46 33 60 00, FAX +46 46 33 66 66
REG. OFFICE ASTRAZENECA AB (PUBL), S-151 85 SÖDERTÄLJE SWEDEN, REG NO 556011-7482, VAT NO SE556011748201

OBJECTIVES

The primary objective of the study was to assess the efficacy of Oxis (formoterol) 9 mg b.i.d., and Accolate (zafirlukast) 20 mg b.i.d. as add on treatments to Pulmicort (budesonide) Turbuhaler 200 mg b.i.d in asthmatics not adequately controlled on inhaled GCS. The primary variable for the analysis of efficacy was the change in morning PEF. Secondary variables were FEV_1, asthma exacerbations and diary card data.

STUDY DESIGN

The study was of a double-blind, randomised, placebo-controlled parallel group designs.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Diagnosis Asthma.

Inclusion criteria: Male or female out-patient, with asthma, aged 12-70 years currently treated for at least 3 months prior to visit 1, with 400-1000 μg inhaled GCS. Patients should have a FEV_1 of 50-80% of predicted normal and show reversibility in FEV_1 ≥12% and at least 200 mL after inhalation of 1 mg terbutaline sulphate. Smoking history of ≤10 pack years. Signed inform consent should be given by the patient.

Exclusion criteria: Respiratory infection, clinical obstructive pulmonary disease or pulmonary dysfunction other than asthma. Other diseases that may interfere with study assessments, as judged by the investigator. Pregnant or lactating women. Use of long-acting β_2-agonist within 1 month prior to visit 1. Previous use ever of a leukotriene antagonist. Known intolerance to any of the study drugs or inhaled lactose.

Criteria for allocation of patient number: The patient should, during the last seven days of run-in, have an asthma symptom score of ≥1 on 4 days or awakening on ≥1 night due to asthma symptoms, and use of β_2-agonist ≥10 puffs as weekly mean. The patient should show competence in using Turbuhaler according to instructions and be compliant in completing diary cards and assessments.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide via Turbuhaler 200 μg/dose, 200 doses. Batch YL 958, AC 1099. Daily dose: 200 μg b.i.d

Formoterol via Turbuhaler 9 μg per delivered dose (12 μg metered dose), 60 doses. Batch ZA 123, Daily dose: 9 μg b.i.d

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Zafirlukast 20 mg per tablet, 56 tablets. Batch DA 944, UM 970D, UN 916, LA 929B. Daily dose 20 mg b.i.d.

Placebo Turbuhaler (formoterol) Lactose 0.6 mg, 60 doses. Batch ZG 34, ZA 33. Daily dose b.i.d.

Placebo tablets (zafirlukast) Lactose 200 mg, 56 tablets Batch DAD 2, DAD 2/2, DYK 1. Daily dose 1 tablet b.i.d.

DURATION OF TREATMENT

Eight weeks

MAIN VARIABLE(S):

- **EFFICACY**

The change in morning PEF was the primary variable

Secondary variables were FEV_1, asthma exacerbations and diary card data

- **SAFETY**

The safety variable was the reported adverse events

STATISTICAL METHODS

The primary efficacy variable was analyzed using an analysis of variance (ANOVA) model and the log rank test was used to analyse “time to first asthma exacerbation”

PATIENTS

At least 300 patients were planned to be randomized into the study

	Bud	**Bud + Zaf**	**Bud + For**	**All**
No. planned	100	100	100	300
No. randomized and treated	116	118	118	352
Males/Females	62/54	55/63	58/60	175/177
Mean age	38.1	38.3	38.1	38.2
Race (n): -Caucasian	115	118	118	351
-Other	1			
BMI (kg/m^2	25.52	26.03	25.15	25.57
-range	15.1-45.0	16.9-43.8	16.8-36.3	15.1-45.0
Duration of Symptoms (years)	10.6	10.1	12.1	10.7
Smokers (n)	4	11	9	24
Baseline Value				
PEF-Morning (L/min), mean	349.5	339.7	330.4	339.8
FEV_1 (% PN)	72.12	72.03	69.71	71.28
Asthma symptoms -nighttime, mean	0.68	0.79	0.71	0.73
Asthma symptoms -daytime, mean	1.07	1.16	1.10	1.11
Rescue use night (occ) mean	0.80	0.93	0.82	0.85
Rescue use day (occ), mean	2.20	2.33	2.23	2.25
Awakenings (% of nights)	50.5	53.1	48.1	50.6
Morning symptoms (% of mornings)	56.5	58.5	54.2	56.4
No. analysed for efficacy	116	118	118	352
No. analysed for safety	116	118	118	352
No. completed	107	99	106	312

SUMMARY - CONCLUSION(S)

- EFFICACY RESULTS

The statistical analysis of the primary variable change in morning PEF, showed no statistically significant difference between BUD+ZAF and BUD+FOR (p=0.5473). A statistically significant difference was detected between BUD+FOR and BUD (p= 0.0186), whereas the difference between BUD+ZAF and BUD only reached borderline significance (p= 0.0781). The analyses of the secondary variables failed to reveal a statistically significant difference between BUD+FOR and BUD+ZAF for any variable, but BUD+FOR was numerically better for all variables

- **SAFETY RESULTS**

All treatments were well tolerated in this study.

DATE OF THE REPORT

December 11, 2000