AstraZeneca

CLINICAL STUDY REPORT

DRUG SUBSTANCE	Budesonide
DOCUMENT NO.	04-CR-3066
VERSION NO.	01
STUDY CODE	04-3066
DATE	16 August, 2000

FINAL

Early intervention with anti-inflammatory treatment of childhood bronchial asthma. A comparison between budesonide and disodium cromoglycate.

STUDY PERIOD:	March 8, 1995 - May 31, 1999.
PHASE OF DEVELOPMENT:	III A
STUDY DESIGN:	Randomized, partly double-blind, controlled, parallel group.
DIAGNOSIS:	Children with newly detected asthma.
TEST DRUG AND DOSAGE:	Budesonide Turbuhaler® 800 μg/day for one month, 400 μg/day for five months and 200 μg/day or placebo for the following twelve months.
COMPARATOR DRUG AND DOSAGE:	Disodium cromoglycate pMDI 30 mg/day for eighteen months.
DURATION OF TREATMENT:	18 months.

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

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AstraZeneca

DRUG PRODUCT	Budesonide Turbuhaler©	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide	REFERRING TO PART OF THE DOSSIER	
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FINAL

Early intervention with anti-inflammatory treatment of childhood bronchial asthma. A comparison between budesonide and disodium cromoglycate.

STUDY CENTRE(S)

Single centre study.

PUBLICATION (REFERENCE)

Not Applicable.

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	March 8, 1995	IIIA
- **DATE OF LAST PATIENT COMPLETED**	May 31, 1999	

OBJECTIVES

Primary objective

- To compare the long-term effects of three treatments (two treatment strategies with inhaled budesonide and inhaled DSCG) on lung function over an eighteen-month study period in children with newly diagnosed asthma. The primary efficacy variable was morning PEF.

Secondary objectives

- To determine whether the long-term effects of the three treatments differ with respect to morbidity, as measured by asthma symptoms, use of rescue β_2-agonist, degree of bronchial mucosal inflammation (sputum inflammatory markers, subpopulation histology), degree of non-specific bronchial hyperresponsiveness to histamine, and consumption of concomitant drugs to control symptoms.

- To determine whether the long-term effects of the three treatments differ with respect to tissue growth as indicated by growth (stadiometry), bone density (X-ray absorptiometry), bone metabolism markers and skin density (sonography).
- To determine whether the long-term effects of the three treatments differ with respect to long-term safety, as indicated by eye examinations and adverse events.

STUDY DESIGN

Randomized, partly double blind, controlled, parallel-group.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Major inclusion criteria:

- Children between 5 -10 years of age with newly diagnosed bronchial asthma.
- Definition of bronchial asthma:
  - a history of asthma symptoms, defined as cough, wheeze and decreased tolerance to exercise at least for one month (as expressed in the national Finnish consensus)
  - not previously having required maintenance treatment or having ever been treated with inhaled corticosteroids for >60 ±5 days.
- The children were to have a diurnal variation in peak expiratory flow (PEF) of >20 % within the last three months preceding Visit 1 or a ≥15% bronchial reversibility as shown either with a bronchodilator test or an exercise test.
- PEF after conventional treatment with an inhaled β_2-agonist was to be ≥ 60% of predicted normal value.
- Median PIF_{TBH} during the last week of run-in should be >40 L/min measured and recorded by Vitalograph DS Spirometer (Visit 2).

Major exclusion criteria:

- Use of inhaled/nasal corticosteroids and oral prednisolone during the two last months prior to Visit 1.
- Inhaled corticosteroids in a total cumulative dose of ≥36 mg.
- Nasal corticosteroids in a total cumulative dose of ≥12 mg.
- Oral prednisolone in a total cumulative dose of ≥200 mg.
- History of eye disease.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide (Pulmicort®) Turbuhaler 400 μg/dose, 200 doses. Batch numbers were: VA 324, XA 397, XK 456, YH 527. Daily dose: 800 μg - one inhalation b.i.d.

Budesonide (Pulmicort®) Turbuhaler 200 μg/dose, 200 doses. Batch numbers were: UK 616, VE 672, XH 819. Daily dose: 400 μg - one inhalation b.i.d.

Budesonide (Pulmicort®) Turbuhaler 100 μg/dose, 200 doses. Batch numbers were: VA 217, XF 263, XL 275, ZB 326. Daily dose: 200 μg - one inhalation b.i.d.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Disodium cromoglycate (Lomudal®) pMDI with Fisonair spacer, 5 mg/dose, 112 doses. Batch numbers were: AAD31D, AAD12E, AAD46E, AAD9G, AAD12G, A61174, A70694, A61970, A70060. Daily dose: 30 mg - two inhalations t.i.d.

Placebo Turbuhaler. Batch numbers were: VC 13, XC 22, XK 25, ZA 28. Daily dose: One inhalation b.i.d.

DURATION OF TREATMENT

Double-blind treatments

Pulmicort Turbuhaler® 400 μg twice daily for 1 month followed by Pulmicort Turbuhaler® 200 μg twice daily for 5 months followed by Pulmicort Turbuhaler® 100 μg twice daily for 12 months.
or
Pulmicort Turbuhaler® 400 μg twice daily for 1 month followed by Pulmicort Turbuhaler® 200 μg twice daily for 5 months followed by placebo Turbuhaler® twice daily for 12 months.

Open treatment

Lomudal® (Fison) pressurized metered dose inhaler (pMDI) with a valved spacer device (Fisonair) 10 mg three times a day for 18 months.

MAIN VARIABLE(S):

- **EFFICACY**

Primary efficacy variable

- Morning PEF recorded at home in Vitalograph Data Storage Spirometers.

Secondary variables

- Lung function, asthma symptoms, β_2-agonist consumption, asthma exacerbations.
- Growth, bone metabolism.
- Clinical chemistry and hematology, immunological investigations in sputum.
- Eye examinations.

- **SAFETY**

- Adverse events.

STATISTICAL METHODS

The (main) analysis followed an intention-to-treat approach. This means that all patients who had taken at least one dose of study medication and had data from the run-in period and the required treatment period(s) were included. Withdrawn patients were handled using last value extended, within period (0-6 months and 7-18 months). All tests were two-sided and p-values below 0.05 were considered statistically significant. For the primary efficacy

variable, morning PEF from the diaries, and most of the secondary efficacy variables, treatment regimens were compared using analysis of variance (ANOVA) models with fixed factor treatment and using baseline as a covariate. The ANOVA models could be either additive or multiplicative (i.e. the analysis is performed on logged values). For variables with a very skew distribution of values, a non-parametric Kruskal-Wallis' test (followed by pairwise Wilcoxon tests) was considered as a complement (laboratory variables). The time to first asthma exacerbation and time to withdrawal were compared between treatment regimens using survival analysis (Kaplan-Meier) and the log-rank test.

PATIENTS

It was planned that 180 newly diagnosed asthmatic children would be randomized. 193 children were enrolled, 182 were randomized and 178 started with study therapy. 59 children were given randomized treatment with budesonide/budesonide, 58 children with budesonide/placebo and 61 children received disodium cromoglycate pMDI.

	Budesonide/ budesonide	**Budesonide/ placebo**	**DSCG**	**Total**
No. planned	60	60	60	180
No. randomized and treated	59	58	61	178
Males/Females	35/24	38/20	34/27	107/71
Age range (years)	5-10	5-10	5-10	5-10
No. analyzed for efficacy	58	58	60	176
No. analyzed for safety	59	58	61	178
No. completed	53	46	45	144

SUMMARY - CONCLUSION(S)

- EFFICACY RESULTS

No statistically significant differences were found between the treatment regimens after either 18 months or 6 months treatment for the primary efficacy variable PEF morning from the daily diaries. No statistically significant differences were found on other lung function variables (PEF evening, FEV_1 morning and evening, $FEV_{0.5}$ morning and evening, FVC morning and evening) after 6 or 18 months treatment. For asthma symptom scores no differences between treatments were found after 6 months treatment. After 18 months treatment the difference between BUD/BUD and DSCG was statistically significant for both day-time and night-time symptoms as well as the difference BUD/BUD versus BUD/ Placebo for day-time symptoms. For the use of rescue medication there was a statistically significant difference in day-time usage between budesonide and DSCG after 6 months treatment, but no differences after 18 months treatment.

For clinic visit spirometry no statistically significant differences between treatments were found after 18 months treatment. After 6 months treatment there was a statistically significant difference between budesonide and DSCG as measured by FEV_1, $FEV_{0.5}$ and $FEF_{50\%}$, but not for PEF and FVC. BUD/BUD and DSCG both gave a statistically significantly higher degree of protection against histamine than BUD/Placebo after 18 months treatment. The incidence of asthma exacerbations was statistically significantly

higher in the DSCG group (2.70) than in the BUD/Placebo (1.92) and BUD/BUD (1.23) group. The difference BUD/BUD versus BUD/Placebo was also statistically significant.

There was a statistically significant difference in change in height (SD scores) between BUD/BUD (-0.20 SD), BUD/Placebo (-0.08 SD) and DSCG (-0.01 SD) after 18 months treatment (both completers and all-patients populations). The difference between BUD/BUD and DSCG was about 1 cm, a difference seen already after 6 months treatment. Growth velocities were similar in the BUD/BUD and DSCG groups during the last 12 months. No statistically significant differences between treatments were found on weight or body mass index.

There was a statistically significant difference between BUD/BUD and DSCG (completers and all-patients) and between BUD/BUD and BUD/Placebo (all-patients) on bone mineral density after 18 months treatment. On skin thickness, left fore-arm, there was a statistically significant difference between budesonide and DSCG after 6 months treatment, but no statistically significant differences between treatment groups after 18 months treatment. Statistically significant differences between budesonide and DSCG after 6 months were seen for all four bone markers (serum osteocalcin, serum P1NP, serum 1CTP and urine deoxypyridinoline). No statistically significant differences between treatments were seen after 18 months treatment.

Hematology, flow cytometry in blood and sputum markers showed a very large spread in data making a non-parametrical analysis preferable. Statistically significant differences were seen between budesonide and DSCG after 6 months and between BUD/BUD and DSCG after 18 months on blood neutrophils and blood lymphocytes. Statistically significant differences were seen on CD19 between budesonide and DSCG after 6 months and on CD8 between BUD/BUD and BUD/Placebo and between BUD/BUD and DSCG after 18 months. No statistically significant differences between treatments were seen on sputum ECP and sputum HNL. A statistically significant difference was seen between budesonide and DSCG after 6 months on sputum squam cells.

No statistically significant differences between treatments were found on intraocular pressure or cycloplegic refraction. The number of reported opacities (cortical - wedges and spokes; nuclear and subcapsular) was low and findings were in most cases not present at a reexamination.

- **SAFETY RESULTS**

A total of 639 adverse events were reported during the study, 215 in the BUD/BUD group, 230 in the BUD/Placebo group and 194 in the DSCG group. Seven serious adverse events were reported during randomized treatment and one post study. All 8 were serious due to hospitalization, and none was considered to be casually related to the investigational drugs. The overall picture is that all three treatment strategies were well tolerated.