AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide Turbuhaler	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	04-CR-3064B		
VERSION NO.	01		
STUDY CODE	04-3064B		
DATE	22 September, 2000		

FINAL

One year open follow-up to study; Effect of one year treatment with budesonide Turbuhaler® and nedocromil pMDI with spacer on bone mineral density, physical activity, and lung function in newly diagnosed asthmatic children.

STUDY CENTRE(S)

Single centre study.

PUBLICATION (REFERENCE)

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STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	April 10, 1997	IV
- **DATE OF LAST PATIENT COMPLETED**	November 18, 1999	

OBJECTIVES

The primary objective was to compare asthmatic children with healthy children regarding bone mineral density.

STUDY DESIGN

Open study with regard to treatment and single-blind with respect to the DEXA (dual energy X-ray absorptiometry) measurements, i.e. the person responsible for the measurement and analysis had no information regarding each child's treatment during the first year, and bone age assessments.

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Asthmatic children and healthy children.
This was a one year follow-up study to the study “Effect of one-year treatment with budesonide Turbuhaler® and nedocromil pMDI with spacer on bone mineral density, physical activity and lung function in newly diagnosed asthmatic children", study code: 04-3064.

All asthmatic children included in the follow-up study must have completed the first double-blind year.

All healthy children had to have completed the first year and have normal lung function at visit 4 to be eligible for the two-year follow-up visit.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide Turbuhaler was prescribed individually to all asthmatic children aiming at giving the lowest maintenance dose possible. The healthy children received no medication.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Not applicable.

DURATION OF TREATMENT

12 months.

MAIN VARIABLE(S):

In asthmatic children: Bone mineral density (BMD) after 12 and 24 months treatment with budesonide Turbuhaler®, depending on randomization during year 1.

In healthy children: BMD after 24 months.

- **EFFICACY**

The primary variable was total body bone mineral density (BMD (g/cm^2) assessed by DEXA. Other variables were bone density by ultra sound, height, weight, lung function, exercise test, exhaled NO, pubertal development, calcium intake, bone age and physical activity. Periodically, asthmatic children daily registered morning and evening PEF as well asthma score and intake of study drug in a diary card.

The same assessments were made for the healthy children with the exception of lung function, exercise test and diary card recordings.

- **SAFETY**

Adverse events were collected.

STATISTICAL METHODS

Growth variables were analyzed using a linear mixed effects model approach where separate estimates of growth per year were obtained for boys and girls in the two treatment groups.

A patient's contribution to the parameter estimates was determined by the time in the study. Efficacy variables were analyzed using a standard ANOVA model with treatment and age class as factors and baseline values as covariates. All patients were analyzed with an Intention to Treat approach to the analyses.

Abbreviations:

BUD-BUD - Budesonide treatment during year one and the follow-up year.

NED-BUD - Nedocromil treatment during year one and budesonide during the follow-up year.

PATIENTS

64 asthmatic children completed study 04-3064. 61 of these gave their signed informed consent to participate in this one year follow-up study. 46 healthy children completed the first year and 38 of these gave their signed informed consent to participate in the 2-year follow-up visit.

Table 1. Demographic summary at the start of year1 and year2

	Start Year 1			Start Year 2		
Variable	BUD-BUD	NED-BUD	Healthy	BUD-BUD	NED-BUD	Healthy.
N	46	45	46	35	26	38
Female/Male	15/31	19/26	24/22	12/23	13/13	21/17
Age (years)	9.3	9.3	9.5	10.5	10.1	10.6
	(7-12)	(7-12)	(8-11)	(8-13)	(8-12)	(9-12)
Height (cm)	135.65	135.96	137.92	141.96	141.85	144.80
	(116.6-155.9)	(116.5-152.1)	(121.3-161.7)	(126.7-161.6)	(123.4-156.0)	(127.6-170.0)
BMD (g/cm^2)	0.89	0.88	0.89	0.91	0.91	0.92
	(0.8-1.0)	(0.8-1.0)	(0.8-1.1)	(0.8-1.0)	(0.8-1.1)	(0.8-1.1)
Morning PEF (% of predicted normal)	85.32	83.34	.	88.04	92.38	.
	(58.1-113.9)	(56.9-116.9)	(.-.)	(70.8-104.9)	(67.4-125.8)	(.-.)
FEV_1 (% of predicted normal.)	101.43	101.94	112.11	104.67	105.26	.
	(72.1-133.5)	(71.5-146.0)	(90.6-140.0)	(59.0-134.3)	(83.3-130.0)	(.-.)
Exercise induced maximal fall in FEV_1 (%)	11.13	15.61	.	2.02	10.73	.
	(-2.6-66.9)	(-2.4-63.3)	(.-.)	(-46.6-21.7)	(0.4-37.1)	(.-.)
NO (ppb)	9.79	13.16	3.85	7.61	10.52	3.46
	(2.0-46.0)	(1.6-68.3)	(1.4-7.7)	(1.7-50.2)	(1.7-50.1)	(0.9-7.5)

SUMMARY

- EFFICACY RESULTS

Total body BMD in asthmatic children treated with budesonide for two years increased in a similar way as compared to healthy children of the same age. In children treated with NED-BUD BMD decreased during the second year as compared to healthy children (p=0.0494) but not so compared to BUD-BUD treated asthmatics.

The changes in % from baseline (start of the study, year 1) in total body BMD were not shown to be different after year1 or year2 when comparing both treatment groups.

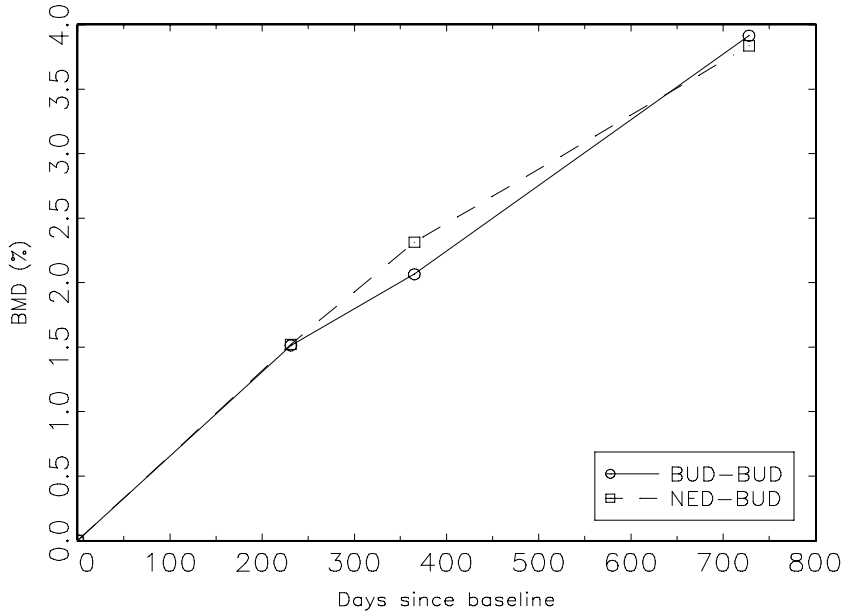

Figure 1. BMD (%), raw mean values of the changes.

Height was delayed in the budsonide group as compared to the nedocromil group during the first months of the study. In the beginning of the follow-up year the difference had decreased and at the end of the second year there was no evidence of any difference in growth between the BUD-BUD and the NED-BUD group. The asthmatic children were estimated to grow 0.6 cm less ($p>0.14$) than the healthy subjects although this was not a statistically significant difference.

During the follow-up year the BUD-BUD children maintained asthma control at the same level as during the first year. An improvement was seen in the NED-BUD children who decreased their maximal fall in FEV_1 after exercise, normalized their levels of NO in exhaled air and increased their mPEF. This was the same pattern that was seen in the BUD-BUD children when budesonide was initiated in the first year.

There was no difference between the groups when comparing asthma symptoms and use of β_2-agonist.

- **SAFETY RESULTS**

A total of 96 AEs were reported during this follow-up study. No deaths were reported. One SAE was reported during the second year, a patient hospitalized due to laryngitis.

No discontinuations due to Adverse Event disease under investigation deteriorated or Adverse Event other were reported. During this follow-up study, no important differences in the AE-pattern was seen between the NED-BUD group and the BUD-BUD group.

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DATE OF THE REPORT

22 September, 2000