Drug Product Pulmicort® pMDI® Drug Substance Budesonide Edition Number 1 Study Code SD-004-0299 Date 08 November 2007	**SYNOPSIS**	(For National Authority Use only

Prevention of asthma in infants/young children - PAC

Publications

Bisgaard et al; Intermittent inhaled corticosteroids in infants with episodic wheezing. NEJM 2006;354:1998-2005.

Study dates

First subject enrolled: 28 August 1998

Last subject completed: 3 December 2004

Phase of Development

Therapeutic use (IV)

Objectives

The primary objective of the study was to investigate the ability of budesonide, given during episodes of troublesome lung symptoms (TLS) to reduce further symptoms in infants and young children at risk of developing asthma, by evaluating:

- Symptom free days (= days with no symptoms)
- TLS (troublesome lung symptoms) -free days (= days with no symptoms and no use of β_2-agonist)
- Rescue-free days (days with no use of short-acting β_2-agonist)
- Number of treated episodes
- Number of treatments with Add-on medication

The secondary objectives of the study was to investigate the ability of budesonide, given during episodes of troublesome lung symptoms to prevent / delay the development of asthma by evaluating:

- The asthma status
- Time to start of algorithm treatment (time to start of evaluation of asthma)
- The total dose of steroid prednisolone and budesonide
- The number of courses of prednisolone

To investigate the acute effect of budesonide during the first treatment episode by evaluating, during the first treatment episode

- The number of symptom days
- The number of days with use of β_2-agonist
- Number of patients who needed add-on medication

To investigate the safety of budesonide by evaluating

- The bone mineral density (BMD), assessed by means of ultrasonographic measurement at the phalanx at 3 years of age
- The height at 3 years of age, measured by stadiometry
- The number of serious adverse events and the number of discontinuations due to adverse events.

Study design

This was a single centre, randomized, parallel group, double-blind, placebo-controlled study including approximately 400 children. The duration of the study was 36 months. Prevention of Asthma in infants/young children“ was a sub-study to the COPSAC study (Copenhagen Prospective Study on Asthma and Allergy in Childhood).

Target subject population and sample size

One major risk factor for developing asthma is a parental (especially maternal) history of asthma and atopy. The COPSAC study aims to investigate the development of asthma, eczema, allergic rhinitis and allergy from infancy through childhood with the overall aim to learn how to prevent these diseases. Infants, born of asthmatic mothers were included in the COPSAC study. The aim of the present study (PAC) was to investigate the preventive effects of budesonide on the development of wheezing and asthma, the target population of this study consisted of infants/children enrolled in COPSAC.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The study medication, Pulmicort pMDI and corresponding Placebo, was administered as two puffs in the evening (total daily dose 400 µg). The treatment was initiated each time the child had 3 consecutive days with any troublesome lung symptoms. The duration of a treatment period was two weeks. Batch numbers: 772-50, 784-50, 791-50, 806-50, AE731, BA750, ZG718, ZK722This procedure was repeated at each episode of troublesome lung symptoms until the infant/young child started treatment according to the algorithm or reached the age of 3 years.

Rescue medication:

Bricanyl pMDI 0.25 mg/dose was dispensed at randomization and used at any time throughout the study. Batch numbers:40950, 445-02, 50050, YE300, YH311, ZM358.

Add-on medication:

If there was an insufficient effect of the study medication the investigator added budesonide 400 µg pMDI in the morning for 2 weeks to the study medication. The child continued with study medication (until the 2 weeks passed as per protocol). If the child still had troublesome lung symptoms, a new 2-week episode with study medication with optional addition of 2 weeks treatment with "add-on" medication was started. In addition, at any time of evaluation, the investigator was free to decide whether ”add-on‘ medication (budesonide 400 µg in the morning for 2 weeks) was indicated. If this was the case, and if necessary, the ”add-on‘ medication was started concomitantly with study medication.

Prednisolone or high dose budesonide courses:

Prednisolone 1-2 mg/kg/day for 3 days, or 1600 µg budesonide pMDI (800 µg b.i.d) for 2 weeks may be given at the discretion of the investigator.

Duration of treatment

Intermittent two week treatments up to the child reached the age of 3 years.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: The primary variable was the number of symptom free days in children treated with budesonide and placebo respectively.

- Secondary variables: Rescue free days, TLS-free days, Asthma status, Time to start of algorithm treatment and time to second treated episode, The total dose of oral steroid and total dose of budesonide, The number of days with symptoms and the number of days with use of β_2-agonist, during the first treated episode, The number of children who needed add-on medication during the first treated episode, Time until the second treated episode

Safety

The safety variables were: the bone mineral density, assessed by means of ultrasonographic measurement at the phalanx at 3 years of age, the height, measured by stadiometry and weight

at 3 years of age, the number of serious adverse events and the number of discontinuations due to adverse event.

Statistical methods

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

Variables relating to the primary objective were calculated during the double-blind period only. For this purpose, the double-blind period was defined to begin on the day of the first intake of study medication and end on the first date of either of study termination, the third birthday, or the date of decision to start algorithm treatment.

Serious adverse events were analysed by means of descriptive methods.

Subject population

A total of 451 patients were enrolled and of these 301 were allocated to treatment. The first patient entered the study on September 23, 1998 and the last patient finished the study on December 3, 2004. A total of 150 children were never randomised and are not included in the analyses regarding treatment comparisons. Of the 301 patients randomised, 7 patients never received treated. Thus 294 were analyzed for safety and 294 were analysed for efficacy in an intention-to-treat analysis.

Table S1 Subject population and disposition

		Active	Placebo	Total
Population				
N randomised and treated		149	145	294
Demographic characteristics				
Sex (n of subjects)	Male	78	82	160
	Female	71	63	134
Age (years)	Mean	11.2	10.3	10.7
	Range	1 to 36 months	1 to 36 months	1 to 36 months
Disposition				
	Randomised	151	150	301
N of subjects who	Completed	135	131	266

(Continued)

Table S1 Subject population and disposition

		Active	Placebo	Total
	Discontin-ued	14	14	28
	Never treated	2	5	7
N analysed for safety[a]		149	145	294
N analysed for efficacy (ITT)		149	145	294

a Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number;

Efficacy results

The primary variable was the proportion of symptom free days during the double-blind study period. Treatment comparisons for the percentage of symptom free days are shown in Table S2 together with the closely linked variables rescue free days, and TLS free days. During the double-blind period, the mean percentage of symptom-free days was similar for the budesonide and placebo groups. Other secondary variables failed to detect differences between the groups

Table S2 Treatment comparison for percentage of symptom free days, rescue free days and TLS free days.

Variable	Treatment	Mean difference	95% C.L.[1]	P-value
Symptom free days (%)	Budesonide 400 µg vs. placebo	1.0	(-4.8, 6.9)	0.72
Rescue free days (%)	Budesonide 400 µg vs. placebo	-2.9	(-6.2, 0.5)	0.090
TLS free days (%)	Budesonide 400 µg vs. placebo	-0.3	(-6.4, 5.7)	0.92

a [1] Confidence limits.

Safety results

Bone Mineral Density (BMD) consists of Bone Transmission Time (BTT) and AD-SoS (Speed of sound), assessed at Visit 7 at 36 moths of age.

Table S3 Treatment comparison for BTT and AD-SoS at 36 months of age

Variable	Treatment	Mean difference	95% C.L.[1]	P-value
BTT (µs)	Budesonide 400 µg vs. placebo	-0.003	(-0.039, 0.033)	0.87
AD-SoS (m/s)	Budesonide 400 µg vs. placebo	-0.2	(-9.3, 9.0)	0.97

a [1] Confidence limits.

Weight and height were also assessed during the study.

Table S4 Treatment comparison for height and weight at 36 months of age

Variable	Treatment	Mean difference	95% C.L.[1]	P-value
Height (cm)	Budesonide 400 µg vs. placebo	-0.13	(-1.17, 0.91)	0.81
Weight(kg)	Budesonide 400 µg vs. placebo	0.34	(-0.10, 0.78)	0.13

a [1] Confidence limits.

In this study only serious adverse events and discontinuations due to adverse events were collected. The mean time of exposure was similar between the groups. During the study 28 of the randomised patients discontinued the study, whereof 1 due to AEs and 27 due to other reasons.

In total 167 SAEs were reported for all enrolled and randomised patients during the study whereof 81 SAEs were reported on treatment with Budesonide and 34 SAEs were reported on treatment with placebo. The majority of the SAEs were of mild to moderate intensity. The frequency of SAEs with severe intensity was low in both treatment groups. The most commonly reported serious adverse events were Respiration abnormal, Pneumonia (including Pneumonia respiratory syntical viral and Pneumonia haemophilus), Febrile convulsions and Gastroenteritis. All the reported SAEs were considered as unrelated to the investigational product as judged by the investigator. The reported SAEs were within the normal pattern for infants.

One patient died during the study (Patient nr 347 /sudden infant death syndrome, placebo), the event was considered unrelated to the investigational product as judged by the investigator.

Table S5 Summary of Serious Adverse Events

	Budesonide 400 µg n=149	placebo n=145	All n=294
No.of Deaths	0	1	1
No. of SAEs other than death	81	33	114
No. (%) of subjects with SAE	42 (28%)	25 (17%)	67 (23%)
Max. No. of SAEs/patient	7	6	7
No. of Other Significant AEs	0	0	0
No. (%) of DAEs	0	1 (1%)	1 (<0.5%)

Table S6 Number (%) of subjects with the most commonly reported[a] serious adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

No. of subjects (preferred term)	Budesonide 400 µg n=149	Placebo n=145	All n=264
Respiration abnormal	11(7%)	6(4%)	17(6%)
Febrile convulsion	9(6%)	3(2%)	12(4%)
Pneumonia	8(5%)	1(1%)	9(3%)
Pneumonia respiratory syntical viral	7(5%)	2(1%)	9(3%)

a Events with a total frequency of ≥3% across all treatment groups are included in this table

Date of Report

08 November 2007