Paediatric Public Assessment Report
EU Work sharing Procedure - Assessment of Paediatric data

Pulmicort Turbuhaler

Powder for inhalation
100 µg, 200 µg, 400 µg
Budesonide

Marketing Autorisation Holder: AstraZeneca

ADMINISTRATIVE INFORMATION

Rapporteur	Germany
Co-Rapporteur	Sweden
Paediatric assessment procedure start date	23.09.2005
Clockstop	22.12.2005 - 27.04.2006
Deadline for Rapporteurs´s final report	28.04.2006
Deadline for members states final comments	23.05.2006
Date of this report:	01.09. 2006

I. RECOMMENDATION

The aim of the "EU worksharing project assessment of paediatric data" is to make the paediatric data available for the European health professionals. Based on the review of the paediatric data on safety and efficacy, the Rapporteur considers that the paediatric indication for Pulmicort (budesonide), in the treatment of asthma that requires treatment with glucocorticosteroids is confirmed. But it is the Rapporteur's opinion that some changes to the SPC might be advisable.

This report should be considered together with the one related to Pulmicort Nebuliser Suspension, which was also considered in this procedure.

II. SCIENTIFIC DISCUSSION

II.3 <clinical aspects>

Pulmicort Turbuhaler was approved in Sweden in 1989 as first European country. It is approved for the treatment of asthma in adult and paediatric patients in more than 90 countries world-wide. It has been approved in most member states of the EU. In Germany Pulmicort Turbuhaler has been approved for children < 12 years with a maximum dose of 800 µg /d. In contrast to Germany, in the US Pulmicort Turbuhaler has been approved for the treatment of asthma in children of ≥ 6 years with the same dose range like in Europe. Additionally the once daily dosing for patients being well controlled on inhaled corticosteroids in the dose ranges 200-400µg was approved in the US as well as in many European countries. For this variation the MAH submitted altogether 13 study-reports with the Pulmicort Turbuhaler not yet submitted to all European countries. Pulmicort Turbuhaler has been nationally approved.

<III.3.1 Clinical pharmacology>

<N/A>

<III.3.2 Clinical efficacy>

Main studies

Study code: 04-3064
Study Phase: IV
Country: Denmark (single-centre)
Study design: Single-centre, randomised, reference-controlled, double-blind, double-dummy, 2 parallel groups
Objective: to compare Budesonide via Turbohaler in a stepwise dosage reduction with nedocromil MDI+spacer on bone mineral density, physical activity and lung function in newly diagnosed asthmatic children aged 7-11 years
Study and control drugs: BUD 200 mcg, 400 mcg; Nedocromil 2 mg/dose
Duration: 12 months (04/96-11/98)
Main inclusion criteria: Asthmatic children aged 7-11 years with a diagnosis of mild and well controlled asthma (according clinical experience) without occasional treatment with oral steroids, Tanner stage < 2.
To compare the growth status a group of healthy volunteers aged 7-11 years with a Tanner stage < 2 was included.
Primary endpoints: Bone mineral density (BMD) measured by dual energy x-ray absorptionmetry and ultrasonic, height by standard deviation score (SDS) and asthma control by measurement of FEV1, PEF, NO, exercise test, exacerbation

No. of randomised patients: N= 91
Mean age: 8.8 years (7-11 years)
Results: No statistically significant difference could be detected in BMD after one year treatment with either BUD or Nedocromil compared with the healthy control group but small differences between treatments.

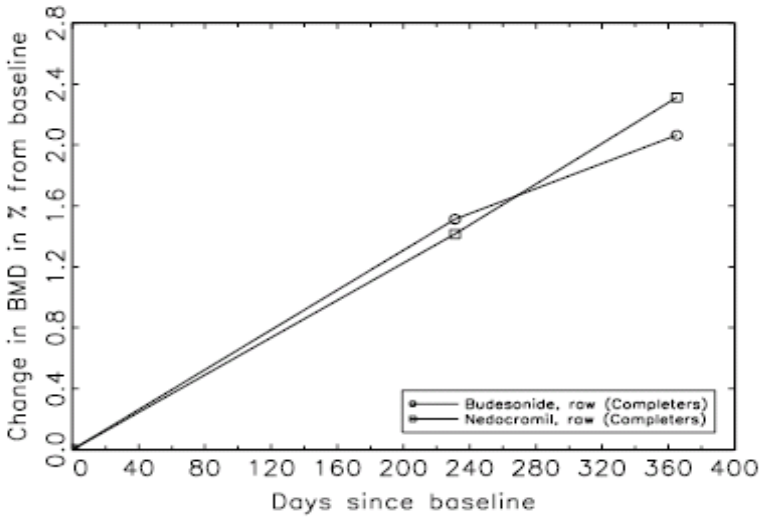


Figure 48. Completers - mean total body BMD, by treatment

There were statistically significant differences in height score between the two treatments after 4 month.

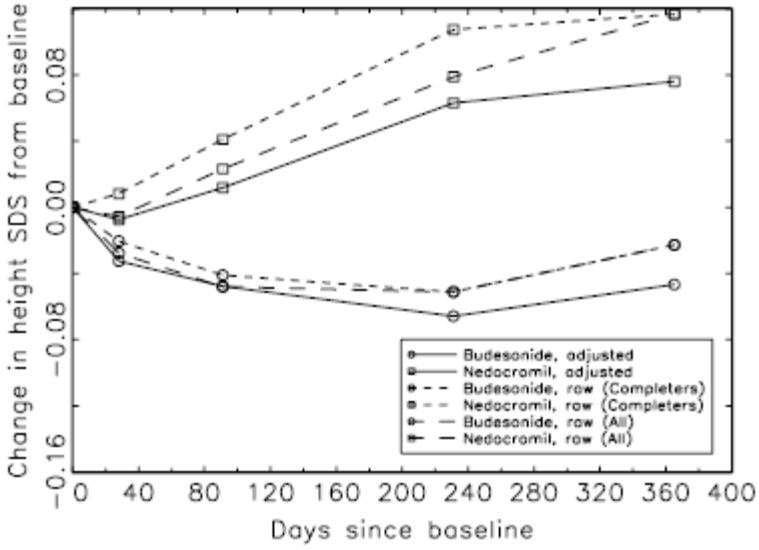


Figure 16. Comparison between different mean height SDS values by treatment. Raw mean values for all patients treated and completers, and mean values for all patients adjusted for age class, gender and baseline values.

For asthma control in the nedocromil group twice as many discontinued the study as compared with the BUD group, exacerbation number was double in the nedocromil group compared with the BUD group and exhaled NO was normalised in the BUD group while no effect was seen in the nedocromil group.
There were no differences in lung function improvement in the two treatment regimes, only the maximum fall in FEV1 after exercise provocation was less in the BUD group.

The number of adverse events was higher in the treatment groups compared to the healthy volunteers but similar in both treatments and none unusual event occurs.

Rapporteur's comment: This trial can be regarded as a safety study in the first line, carried out to show the effect of BUD on growth. It confirmed the now well known effect of growth retardation in combination with corticosteroid treatment in children.
Although the results in asthma control are limited due to the near normal lung function at baseline the trial confirms an advantage of BUD compared to nedocromil with regard to inflammation and exacerbations prevention.
A direct comparison of the treatment groups with the healthy volunteers would have been helpful to interpret the results better.

Co-Rapporteur's comment: Study 04-3064 is another study of six comparing Pulmicort Turbuhaler and cromones, in this case Nedocromil. This study has a double-blind, double-dummy design and had important safety measures on bone mineral density (BMD) and height. BMD was not affected after one year of budesonide treatment. There was a statistically significant effect on growth in the budesonide group after 4 months but not after 12 months, see figure 16 and tables 26, 27 below (from Study Report).
(SDS=standard deviation score)

Study code: 04-3086
Study Phase: IV
Country: Denmark
Study design: Randomised, active-controlled, double-blind, 2 parallel groups
Objective: to compare the minimal effective dose of BUD and FP after stepwise dosage reduction in asthmatic children aged 5-16 years.
Study and control drugs: BUD 100 mcg and 200 mcg /dose, FP (fluticason propionate) 100 mcg
Duration: 15 weeks (08/94-05/95)
Primary endpoints: Minimal effective dose (MED), dose reduction in number of dose steps, morning and evening PEF, asthma symptoms, use of study and rescue medication, Cortisol, AE
No. of randomised patients: N= 217
Mean age: 10.0 years (5-16 years)
Main inclusion criteria: Diagnosis of asthma according ATS, treatment of asthma with 400-800 mcg BUD as the lowest effective dose assessed by the investigator (according BTS-guidelines)
Results:
Efficacy: No statistically significant difference was seen in number of dose reduction steps of in minimal effective dose between the treatments. Similarly, no statistically significant difference was seen for morning PEF.

Table 19. Change in visit variables compared to baseline. (Visit 3 compared to visit 2).

Variable	Treatment	Dose group	n	Mean	SD	Range
FVC (L)	BUD	All	107	<0.1	0.2	(-0.7)- 0.5
	FP	All	107	<0.1	0.2	(-0.6)- 0.6
FEV_1 (L)	BUD	All	107	<0.1	0.2	(-0.6) - 0.5
	FP	All	107	0.1	0.2	(-0.6) - 0.6
$FEF_{25-75\%}$ (L/s)	BUD	All	107	<0.1	0.4	(-1.8) - 0.8
	FP	All	107	0.1	0.3	(-0.6) - 0.9
PEF (measured at clinic) (L/min)	BUD	All	107	10.9	33.1	(-94.0) - 96.0
	FP	All	107	11.6	39.0	(-123.0) - 135.0
Max fall FEV_1 (after exercise) (L)	BUD	All	106	-0.7	8.6	(-27.9) - 27.0
	FP	All	103	-2.5	10.3	(-29.3) - 51.9
Max fall $FEF_{25-75\%}$ (after exercise) (L/s)	BUD	All	106	-1.2	13.8	(-37.2) -34.6
	FP	All	103	-1.2	21.2	(-35.6) - 150.6

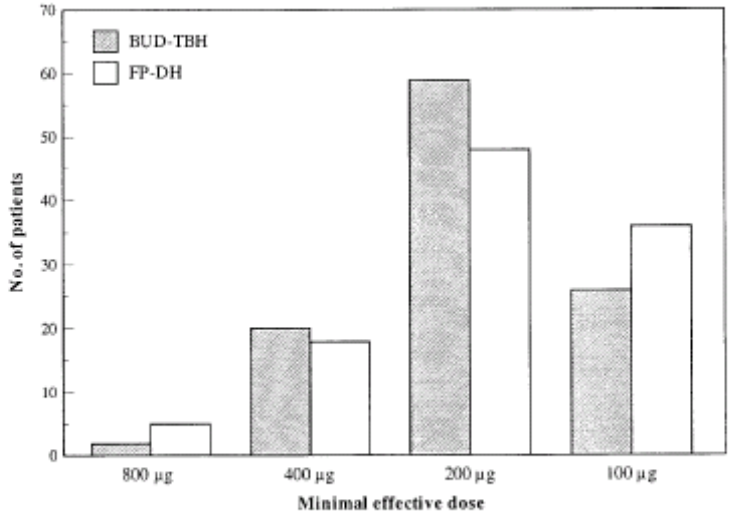


Figure 6. Number of patients at each MED.

Safety: Urinary cortisol or AE-profiles were similar between treatments.

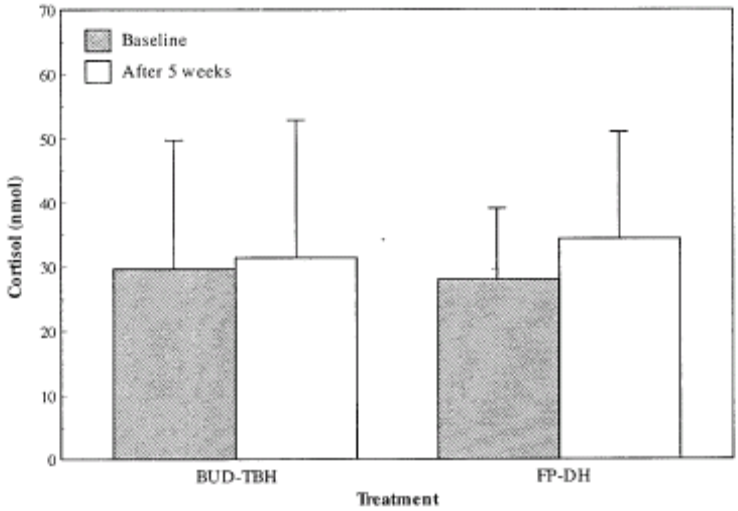


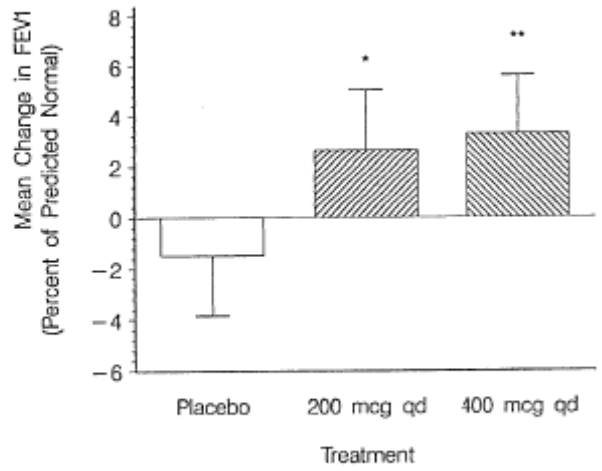
Figure 7. Difference in 24-hour urinary cortisol after 5 weeks (visit 3) and baseline (visit 2)

Rapporteur's comment: This study confirms the expected similar efficacy and safety of BUD and FP. Interesting is that although 400-800 mcg BUD was assessed as the minimal effective dose to control asthma in the included patients a stepwise reduction was nearly for all patients possible so that the majority of patients manage with doses of ≤ 200 mcg BUD. This result is comparable with the findings in adults.

Co-Rapporteur's comment: Study 04-3086 compared the same doses of budesonide and flutide and showed no difference in the minimal effective dose, 188 mcg for budesonide and 180 mcg for fluticasone. Dose equivalence studies are difficult to assess and is not of particular interest for this procedure.

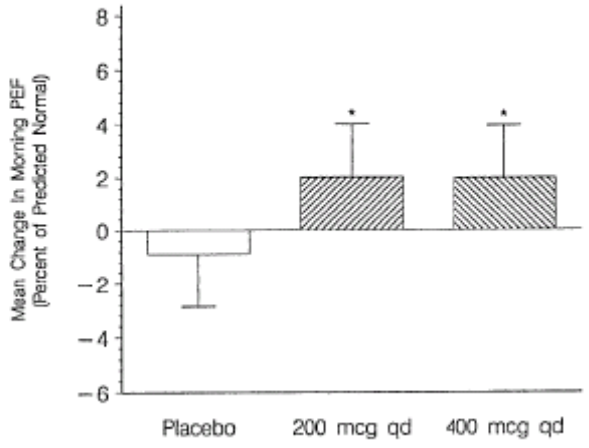
Study code: SD-004-0280
Study Phase: III
Country: USA
Study design: Randomised, double blind, placebo-controlled, 3 parallel groups
Objective: to compare two BUD doses in a once a day dosing regime in children with previous ICS treatment
Study and control drugs: BUD 200 mcg once daily (OD), BUD 400 mcg OD, PLAC
Duration: 12 weeks (03/97-12/97)
Primary endpoint: FEV1
No. of randomised patients: N=274
Mean age: 12.1 years (6-18 years)
Main inclusion criteria: diagnose of asthma according ATS for at least 6 months, treatment of ICS for 16 week immediately before study entry, constant ICS doses for 4 weeks, positive reversibility test, FEV1 ≥65% and ≤90% predicted
Results:
Efficacy: There was a greater increase in FEV1, morning and evening PEF and less usage of rescue medication and less asthma symptoms in the treated patients compared to the placebo group and similar values in both verum groups.

Mean Change# from Baseline to Weeks 2 – 12 in FEV1(Percent of Predicted Normal) ± 95% C.I.
Intent to Treat Analysis, Last Value Carried Forward

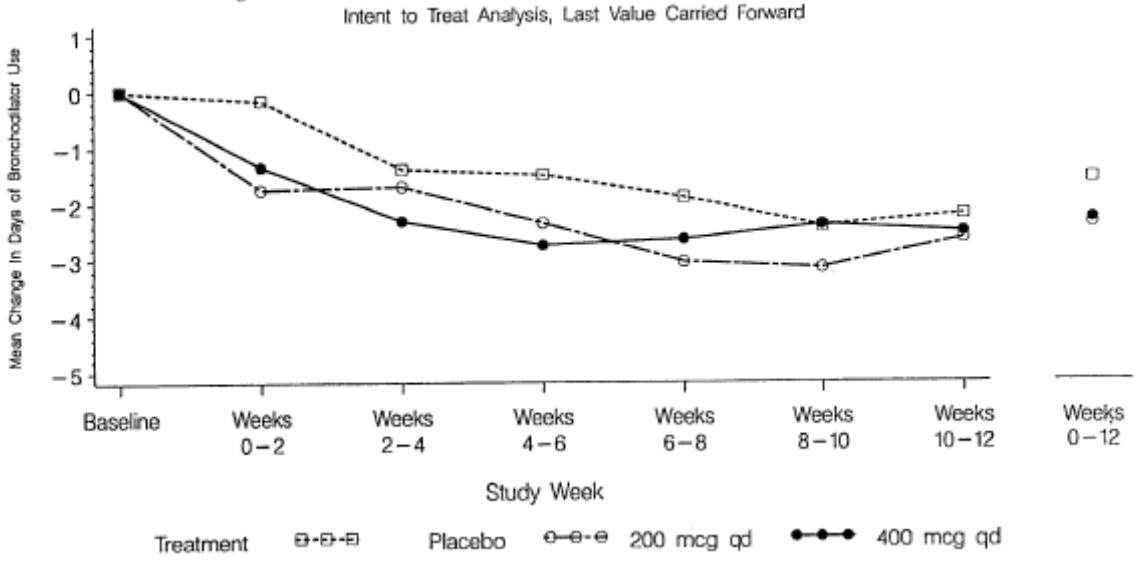


Means Adjusted for Center Effect
* p<= 0.050, ** p<= 0.010, *** p<= 0.001 versus Placebo

Mean Change# from Baseline to Weeks 0 – 12 In Morning PEF (Percent of Predicted Normal) ± 95% C.I.
Intent to Treat Analysis, Last Value Carriec Forward



Mean Change From Baseline to Double – Blind in Bronchodilator Use (No. of Days Used)
Intent to Treat Analysis, Last Value Carried Forward



Safety: The occurred AE´s were listed and were similar in number and organ distribution in all included groups. 4 serious AE´s were reported, two in the PLAC and 2 in the BUD 400 mcg group.

Rapporteur's comment: While the spirometry parameters increase with the ICS treatment, the values decrease in the placebo control. Although the differences are low it shows a tendency to keep asthma under control even with a once daily dosing of ICS in contrast to the deterioration of asthma under placebo treatment.

Co-Rapporteur's comment: All patients had been treated with an inhaled corticosteroid for at least 16 weeks before study enrolment. The inhaled corticosteroids used were triamcinolone (39%), beclomethasone (30%) and fluticasone (22%), the majority on a twice-daily regimen.

Supporting studies:

Study code: 04-3034
Study phase: IV
Country: Sweden
Study design: Randomised, reference-controlled, open, 2 parallel groups
Objective: to compare Budesonide via Turbohaler with DSCG with regard to the cost/benefit ratio in the treatment of asthma in children 4-11 years of age
Study and control drugs: BUD 200 mcg/dose one or two puffs BID (during randomisation), BUD 200 mcg one puff BID or DSCG 20 mg three times a day (during study)
Duration: 12 months (12/92-09/94)
Main inclusion criteria: Children with diagnosed asthma judged by the investigator whom require maintenance treatment with ß-agonists or have night time asthma symptoms and require either DSCG or ICS judged by the investigator.

Primary endpoints: FEV1, PEF, asthma symptoms
No. of randomised patients: N=138
Mean age: 7.3 years (4-11 years)
Results:
Efficacy: No differences were observed between the two treatment groups according FEV1, asthma symptom score, PEF was a little better in the BUD group. The greatest differences were seen with discontinuation of the study due to lack of effect: 25% of the DSCG treated and none of the BUD treated discontinued.

Table 10: *Mean "Well-being scores", measured by the Visual Analogue Scale (VAS).*

Var.:		Pulmicort Group					Lomudal Group				
		N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
VAS well-being (0-100)	Visit 2	69	81.8	17.3	33	100	69	82.8	16.6	16	100
	Visit 7	66	84.0	18.5	32	100	66	85.9	13.6	43	100
	Diff.	66	2.3	21.4	-59	61	66	2.7	21.0	-34	67
	Diff. LVCF	68	0.6	23.7	-78	61	69	3.4	20.9	-34	67

Table 14: *Morning PEF.*

Var.:		Pulmicort Group					Lomudal Group				
		N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
PEF Morning (L/min)	Run-in	69	259.0	67.2	135.3	459.0	69	232.5	59.3	128.8	448.6
	Month 12	65	307.4	78.7	146.0	490.5	64	263.2	64.4	151.4	450.7
	Last 30 d	68	306.0	76.8	152.5	471.7	69	263.9	65.2	151.7	472.0
	Diff. LVCF	68	47.6	44.1	-84.4	206.1	69	31.4	30.8	-43.6	114.0

Safety: There were 7 cases of SAE´s but none of them classified as drug related, no deaths, and two discontinuations due to AE´s in the DSCG group. A detailed analysis of number and organ classes was not submitted.

Rapporteur's comment: The aim of this study was to compare the costs of two treatment schedules as close to real life as possible. Therefore the investigator can alter the doses and treatments to keep asthma control .Patients were only looked at by a doctor in half a year intervals so that a close observation of treatment effects was not possible.

Co-Rapporteur's comment: Study 04-30345 is one of six studies comparing Budesonide Turbuhaler with cromones. This is an open study designed preferably for marketing purposes and not of particular interest for this application.

Study code: 04-3066
Study Phase: III A
Country: Finland
Study design: Randomized, partly-blinded (between BUD groups), 3 parallel groups
Primary objective: to investigate the early intervention with ICS compared to treatment with DSCG in new diagnosed paediatric asthmatics and compare two different step down regimes.
Study and control drugs: BUD 100 and 200 mcg/dose with a stepwise dosage reduction to either 200mcg/day (BUD/BUD) or placebo (BUD/PLAC), DSCG 10 mg
Duration: 18 months (03/95-05/99)
Primary endpoints: Spirometry, PEF, asthma symptoms, use of rescue medication, histamine test, height, BMD, eye opacity, AE´s.
No. of randomised patients: N= 176
Mean age: 6,9 years (5-10 years)
Main inclusion criteria: -newly diagnosed asthma (defined as cough, wheeze, intolerance of exercise) for at least 1 month (according finish consent), PEF variability <20%, pos. reversibility test
Results:
Efficacy: No statistically significant differences were found between the treatment regimes after either 18 months or 6 months treatment for the variables measured at home, except for asthma symptoms after 18 months that showed significant differences in favour of the BUD treatment. There were also statistically significant differences between BUD and DSCG for FEV1, FEV0,5 and FCF 50% measured in clinic but not for PEF and FCV. The BUD/BUD and the DSCG group showed a statistically higher degree of protection against histamine than the BUD/PLAC group.

Table 17. PEF morning (L/min), period means, ITT population

Treatment	N	Run-in	1 month	6 months	12 months	18 months
BUD/BUD	55	183.9	195.7	195.7	201.0	202.5
BUD/PLAC	56	175.7	185.9	194.4	189.8	197.2
DSCG	48	183.9	190.6	198.3	204.5	209.8

Table 20. FEV_1 morning (L), period means, ITT population

Treatment	N	Run-in	1 month	6 months	12 months	18 months
BUD/BUD	55	1.44	1.51	1.54	1.63	1.67
BUD/PLAC	56	1.32	1.42	1.48	1.46	1.53
DSCG	48	1.39	1.44	1.52	1.53	1.63

Safety: The number of reported opacities was low and findings were in most cases not present at a re-examination. There was a statistically significant difference in change in height for all groups.

A total of 639 AE´s were reported during study with a similar number in all treatment groups, 8 serious AE´s occurred but none was considered to be casually related to the investigational drugs.

Table 164. Analysis of height (cm), completers

Treatment	18 months					12 months				
contrast	N	Δ	95% C I		p-value	N	Δ	95% C I		p-value
BUD+BUD	50	7.75	7.34	8.17		50	4.75	4.43	5.07	
BUD+PLAC	45	8.19	7.75	8.63		45	4.89	4.54	5.23	
DSCG	43	8.78	8.34	9.22		43	5.77	5.42	6.11	
B+BUD - B+PLAC		-0.43	-1.04	0.17	0.155		-0.14	-0.61	0.33	0.559
B+BUD - DSCG		-1.02	-1.63	-0.42	0.001		-1.02	-1.49	-0.55	0.000
B+PLAC - DSCG		-0.59	-1.21	0.04	0.064		-0.88	-1.36	-0.39	0.000

Rapporteur's comment: Remarkable in this study is the difference between the home measurements and the ones in the clinic and the indifference of PEF as well at home as in clinic. The lack of differences in PEF is explained by the MAH with the close to normal lung function at baseline. Although PEF is thought to be of equal validity compared to FEV1 and is mentioned as more practical and more convenient for children, these results may initiate a discussion if FEV1 is the more reliable parameter in children and that this may not or not only caused by the better compliance at clinic.
For the effect on growth this study confirms the decrease in BMD due to ICS treatment compared to DSCG.

Co-Rapporteur's comment: This study is one of six studies comparing Pulmicort Turbuhaler with cromones. The study results are interesting from a safety point of view, important measures were performed on BMD, height and eye examinations.

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, figure 39 below.

In the Study Report (page vi), the result on BMD is expressed somewhat different than above; "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." The results are presented in table 72 below.

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.

Study code: 04-9317
Study Phase: IV
Country: UK
Study design: Randomised, double blind, double dummy, 2 parallel groups
Objective: to compare two different dosage regimes of BUD with regard to efficacy in asthmatic children aged 5-12 years
Study and control drugs: BUD 200 mcg BID, 400 mcg once daily
Duration: 8 weeks (11/94-04/97)
Primary endpoints: morning PEF diary
No. of randomised patients: N=167
Mean age: 9,3 months (5-12 months)
Main inclusion criteria: Children 5-12 years of age with a well controlled asthma (no symptoms, PEF> 90% of personal best) treated with ICS on a constant dose of 400 mcg/day for at least 3 month and using SABA as

reliever medication. ICS dose was halved during screening period so that patients become symptomatic. Included were also steroid-naïve patients or using ≤ 200 mcg ICS and being symptomatic.
Results:
Efficacy: Both regimes produced improvements in morning and evening PEF and all other variables recorded at home and at the clinic. There was no difference in the rate of withdrawal between the regimes.

Table 28: Association between previous steroid use and change in morning PEF (absolute change, L/min)

		Budesonide 200µg bd		Budesonide 400µg nocte		P-values
		Baseline	Change to 8 weeks	Baseline	Change to 8 weeks	
STEROID USERS						
Morning PEF	Mean ± SD	246.5 ± 75.3	+14.0 ± 25.6	256.9 ± 49.4	+10.6 ± 34.3	p=0.6394
	N	41	41	27	27	
	Min - Max	121.4 - 410.0	-32.1 - +66.4	165.0 - 366.7	-44.3 - +85.2	
NON-STEROID USERS						
Morning PEF	Mean ± SD	252.2 ± 63.7	+16.5 ± 25.9	240.5 ± 57.8	+33.4 ± 30.5	p=0.0064
	N	44	44	43	43	
	Min - Max	125.7 - 405.0	-38.6 - +78.6	122.9 - 342.9	-22.4 - +100	

steroid user defined as use of inhaled or oral steroids within the 6 months prior to entry

Analysis of variance p-values: Treatment: p=0.1533
Previous steroid use: p=0.0080
Treatment x steroid use interaction: p=0.0322

Safety: There was no apparent difference between the regimes in the number of patients reporting any AE´s and multiple AE´s on in the number of patients reporting adverse events in any body class.

Rapporteur's comment: This study underlines the option for patients being well controlled on ICS to change dose regime from BID to the more convenient once a day regime. Remarkable is the difference in PEF increase between the steroid-naïve and the ICS pre-treated patients. There was no difference in PEF due to dosing regime in the pre-treated group but in the steroid-naïve.

Co-Rapporteur's comment: This study compared once and twice daily use administration of Pulmicort. This dose regimen is approved in Sweden, in several EU countries and in the US. This issue will not be discussed in this application.

Study code: MA-004-0017
Study Phase: IV
Country: Hungary
Objective: to compare BUD with DSCG treatment in asthmatic children
Study design: Randomised, open, active-controlled, 2 parallel groups
Study and control drugs: BUD 200 mcg BID, DSCG 40 mg QID
Duration: 12 weeks (11/96-03/98)
Primary endpoint: morning PEF
No. of randomised patients: N= 171
Mean age: 10.7 years (6-16 years)
Main inclusion criteria: diagnoses of asthma (defined by recurrent episodes of wheezing, breathlessness, chest tightness, cough, airflow limitation), FEV1 > 60% predicted. Patients were treated with DSCG 20 mg QID during run-in period so that all should become symptomatic. Reversibility test had to show 12% FEV1 increase.
Results:

Efficacy: Statistically significant differences were recorded for morning and evening PEF, use of rescue medication in favour of BUD. Differences regarding FEV1 and FCV were seen but not statistically significant.

PEF IN THE MORNING /DIARY/ - PER PROTOCOL POPULATION

TREATMENT	STAT	RUN_IN	PERIOD_1	PERIOD_2
PULMICORT	mean	271.91	296.08	307.92
	standard deviation	82.01	95.07	101.94
	CV	30.16	32.11	33.11
	minimum	122.50	44.17	142.50
	maximum	491.85	532.56	724.52
	n	67.00	66.00	66.00
INTAL	mean	263.15	271.13	269.82
	standard deviation	89.61	93.12	87.72
	CV	34.05	34.34	32.51
	minimum	115.36	116.98	130.12
	maximum	540.74	560.83	548.82
	n	61.00	61.00	61.00

DAILY ASTHMA SYMPTOMS /DIARY/ CHANGE FROM BASELINE - INTENTION-TO-TREAT POPULATION

TRATMENT	STAT	PERIOD_1	PERIOD_2
PULMICORT	mean	-0.18	-0.21
	standard deviation	0.32	0.30
	CV	-179.87	-142.77
	minimum	-1.16	-1.21
	maximum	0.70	0.30
	n	66.00	66.00
INTAL	mean	-0.06	-0.10
	standard deviation	0.30	0.41
	CV	-510.76	-400.20
	minimum	-0.68	-0.96
	maximum	1.17	1.50
	n	64.00	61.00

Safety: Frequency of AE´s was higher in the BUD group but the occurred AE´s are listed, no deaths, two serious AE`s classified as unlikely related to treatment.

Adverse Events in Pulmicort Group, Run-in Period

AEDTXT	Frequency	Percent	Frequency	Percent
Bronchitis	4	23.53	4	23.53
Fever	3	17.65	7	41.18
Pharyngitis	2	11.76	9	52.94
Wheezing	2	11.76	11	64.71
Diarrhoea	1	5.88	12	70.59
Itching Localized	1	5.88	13	76.47
Respiratory Infection	1	5.88	14	82.35
Rhinitis	1	5.88	15	88.24
Sneezing	1	5.88	16	94.12
Tonsillitis	1	5.88	17	100.00

Adverse Events in Intal Group, Run-in Period

AEDTXT	Frequency	Percent	Frequency	Percent
Pharyngitis	2	20.00	2	20.00
Bronchitis	1	10.00	3	30.00
Cephalalgia	1	10.00	4	40.00
Conjunctivitis	1	10.00	5	50.00
Hayfever	1	10.00	6	60.00
Headache	1	10.00	7	70.00
Nose Runny	1	10.00	8	80.00
Vomiting	1	10.00	9	90.00
Wheezing	1	10.00	10	100.00

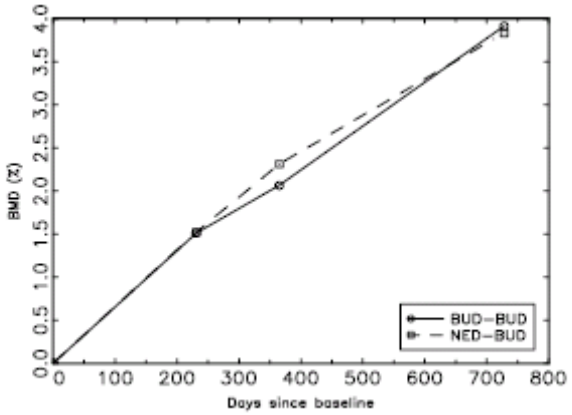
Rapporteur's comment: .Although it was an open trial and therefore interpretation of the results is limited, the advantage of BUD in this efficacy study was expected. The higher rate of AE´s in the BUD group must be kept in mind but was more likely related to the underlying disease than to the drugs.

Co-Rapporteur's comment: This is a further study comparing budesonide and disodium cromoglycate, with an open study designed, preferably for marketing purposes and not of particular interest for this procedure.

<III.3.3 Clinical safety>

The MAH did not give a summary on the submitted trials concerning patient exposure, adverse events and so on. Therefore the studies conducted mainly to establish safety are summarised below.

Study code: 04-3064B
Study Phase: IV
Country: Denmark
Study design: open, not active controlled, follow up study of 04-3064
Objective: one year follow up: effect on bone density, physical activity and lung function when all patients are treated with BUD (either switched or continued treatment)
Study and control drugs: BUD at individually lowest effective dose
Duration: 12 months (04/97-11/99)
Primary endpoints: Bone mineral density (BMD) measured by dual energy x-ray absorptionmetry and ultrasonic, height by standard deviation score (SDS) and asthma control by measurement of FEV1, PEF, NO, exercise test, exacerbation.
No. of randomised patients: N= 61
Mean age: 10,3 years (8-12 years)
Main inclusion criteria: completion of study 04-3064; same like in study 04-3064
Results:
Efficacy: BMD in asthmatic children treated with BUD for two years increased in a similar way as compared to healthy children of the same age. Children treated during the first year with nedocromil and the second year with BUD decreased during the second year as compared to healthy children but not compared with the children treated for two years with BUD.
During the second year the children treated for two years with BUD continued to maintain good control of asthma. The children switched form nedocromil to BUD improved in the response to exercise, increased on morning PEF and showed normal level of exhaled NO.
No deaths were reported. 96 AE´s occurred, one SAE but no discontinuation due to AE´s due to deterioration of asthma were reported.



Rapporteur's comment: This follow up demonstrates that the decrease of BMD is reproducible. The switched patients show the same decrease in BMD in the second year as the BUD treated in the first.
Although the increase in BMD in the second year of the BUD group does not differ from the healthy it increases on a lower level. The AEs are reflected in the SPC of BUD . The remaining frequencies and nature of AEs are comparable between groups with no unexpected AEs in both groups.

Co-Rapporteur's comment: This is an open extension to study 04-3064. The effects on BMD and height are illustrated in the Figures 5 and 7 below (from Study Report). Compared with the group of healthy children, the growth velocity of asthmatic children was reduced by 0.6 cm, however the difference was not statistically significant.

Study code: D5254C00007
Study Phase: IIIb
Country: USA (22 sites)
Study design: composite report of the 5 years open-label extension studies (one GHBA-168 was a pediatric)
Objective: to assess the long-term safety and tolerability of the individual maintenance dose of BUD in a range between 200 and 800 mcg/day in patients with ICS dependent asthma.
Study and control drugs: BUD 100 mcg, 200 mcg/dose
Duration: 5 years (08/92-04/98)
Primary endpoints: some kind of AE´s (e.g. SAEs, deaths, discontinuation due to AE´s)
No. of randomised patients: N= 18
Mean age: 10.3 years (6-18 years)
Inclusion criteria: completion of the 52 weeks open-label extension of study GHBA-168
Results:
Safety: 98 AE´s occurred. 4 serious AE´s were reported, three of them were asthma deteriorations, of which one leads to discontinuation, the fourth was a flu like syndrome. None of the AE´s were unlisted, all patients recovered except the discontinuation case none of the AE´s was attributed to study treatment. No deaths occurred.

Table 17 **Summary of patients with adverse events reported during the extension, sorted by decreasing order of frequency (pediatric population)**

COSTART preferred term	Protocol GHBA-168 (N=18)
Most commonly reported[a] AEs, n and % of patients	
Respiratory infection	11 (61.1)
Pharyngitis	8 (44.4)
Sinusitis	6 (33.3)
Asthma	4 (22.2)
Fever	4 (22.2)
Headache	4 (22.2)
Injury	3 (16.7)
Otitis media	3 (16.7)
Abdominal pain	2 (11.1)
Flu syndrome	2 (11.1)
Myalgia	2 (11.1)
Nausea	2 (11.1)
Rash	2 (11.1)
Vomiting	2 (11.1)

[a] Incidence of adverse events in ≥10% of the pediatric population.
Data from Table 11.3.2.5.

Efficacy: Although FEV1 had been measured during study to demonstrate stable asthma control no results were submitted.

Rapporteur's comment: This study was carried out as an extent of an extent of a blinded trial mostly in view of bridging the time till FDA approval to enable patient maintenance treatment with Pulmicort DPI. Therefore this trial is more like a smaller PSUR than a strongly investigated trial
It is as well noteworthy that only 5 patients completed the study. It can be speculated that prescription ended with improvement of asthma.

Co-Rapporteur's comment: This was an open-label extension after the US pivotal clinical studies for 5 years.

Study code: SD-004-0111 (START)
Study Phase: IV
Country: Multinational
Study design: Multi-centre, multinational, Part A: randomized, double-blind, placebo-controlled, 2 parallel-groups; Part B: open-label, uncontrolled
Objective: to assess effect of early intervention with long-term BUD in newly diagnosed asthma
Study and control drugs: BUD 200 mcg OD, PLAC
Duration: Part A:3 years; Part B: 2 years (09/96-02/03)
Primary endpoints: time to the first serious AE (SAE), change in post bronchodilatator FEV1
No. of randomised patients: N= 1974 < 11 years of age; N=1221 >11 years of age
Mean age: 8.3 years (4-11 years); 13.9 (11-17 years)
Inclusion criteria: Diagnosis of asthma within the 2 years prior study entry verified by symptoms and reversible airway obstruction (either post bronchodilatator FEV1 increase >12%, post exercise FEV1 fall ≥15%, PEF variability >15% in 14 days)
Results:
Safety: There were similar frequency of AE´s in verum and placebo group, most frequently reported AE´s all listet, 2 deaths occurred in the children population, both unlikely related to study drugs.

Table 25 Most frequently reported adverse events, by system organ class, Part A. Number (%) of patients reporting at least one AE in a SOC after first dose of investigational product

System organ class	Pulmicort (N=3630)		Placebo (N=3591)		Total (N=7221)	
	N	(%)	N	(%)	N	(%)
Respiratory system disorders	2437	-67%	2420	-67%	4865	-67%
Resistance mechanism disorders	886	-24%	817	-23%	1703	-24%
Body as a whole - general disorders	852	-23%	822	-23%	1674	-23%
Gastro-intestinal system disorders	780	-21%	684	-19%	1464	-20%
Skin and appendages disorders	483	-13%	480	-13%	963	-13%
Centr & peripher nerv syst disord	468	-13%	439	-12%	907	-13%
Musculo-skeletal system disorders	311	-9%	316	-9%	627	-9%
Vision disorders	267	-7%	244	-7%	511	-7%
Reproductive disorders, female	160	-4%	141	-4%	301	-4%
Psychiatric disorders	124	-3%	152	-4%	276	-4%

There were some AE´s more frequently observed in connection with BUD but these data was not stratified by age so that no conclusion can be made on the paediatric population. In the BUD group no causally treatment related SAE occurred in the paediatric population.
The 3-year growth in the BUD group was statistically significant retarded. This treatment effect was more pronounced in the first year and becomes subsequently smaller.

Table 54 Yearly growth (cm) in children of age <11 years at baseline

tmt	SEX	Variable	N	Mean	Std Dev
Placebo	**Male**	Year 1	499	5.57	1.95
		Year2	479	5.57	3.08
		Year 3	463	6.17	3.31
		Year 4	447	5.78	2.44
		Year 5	439	6.11	2.83
	Female	Year 1	352	5.89	2.20
		Year 2	336	6.00	2.08
		Year 3	323	5.81	2.31
		Year 4	308	4.95	2.48
		Year 5	300	3.93	3.48
Pulmicort	**Male**	Year 1	537	4.93	1.97
		Year 2	509	5.23	2.14
		Year 3	497	5.74	2.24
		Year 4	483	6.28	2.39

(Continued)

Table 54 Yearly growth (cm) in children of age <11 years at baseline

tmt	SEX	Variable	N	Mean	Std Dev
		Year 5	478	6.07	2.61
	Female	Year 1	348	5.22	2.25
		Year 2	328	5.43	2.26
		Year 3	317	5.54	3.36
		Year 4	293	4.98	2.79
		Year 5	290	4.26	3.30

Efficacy: The risk for a severe asthma related event was in the BUD group nearly halved compared to placebo. FEV1 increased, asthma symptoms and use of rescue medication decreased in the BUD group during the Part A of the study. In Part B open-label, when all patients received BUD values of both groups drew near.

Figure 19 **First severe asthma-related event**

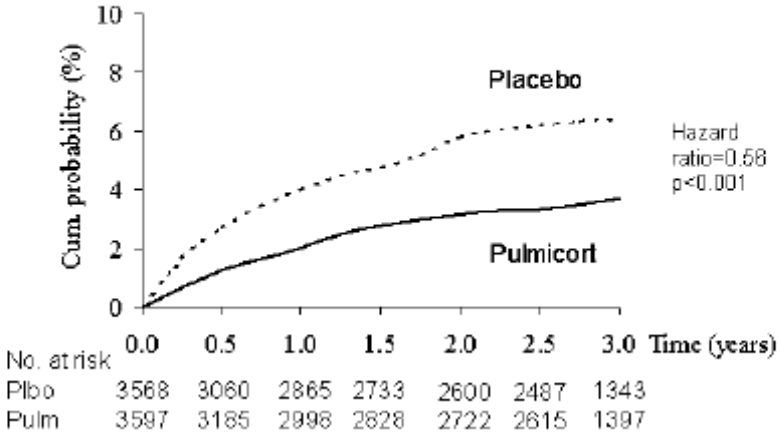
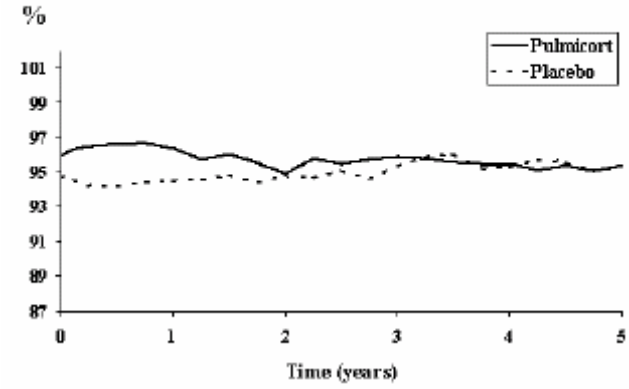


Figure 25 **Post-bronchodilator FEV_1 % predicted. Children: age ≤10 years (completers).**

Post-bronchodilator FEV_1 % predicted. Adolescents: age 11-17 years. (completers)

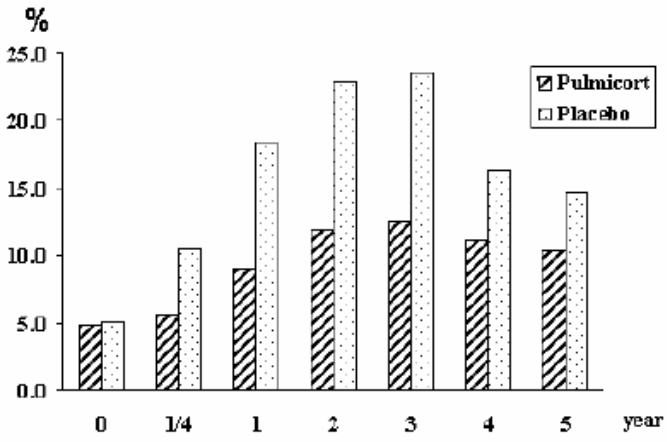


Rapporteur's comment: The relevance of this study is reduced by the fact that all patients should continue their normal asthma medication (nearly 25 % of the placebo and 15% of the BUD group uses additional ICS in the third year of the study; >60% of all patients use SABA).So, significance of post dilatator FEV1 can be doubted.

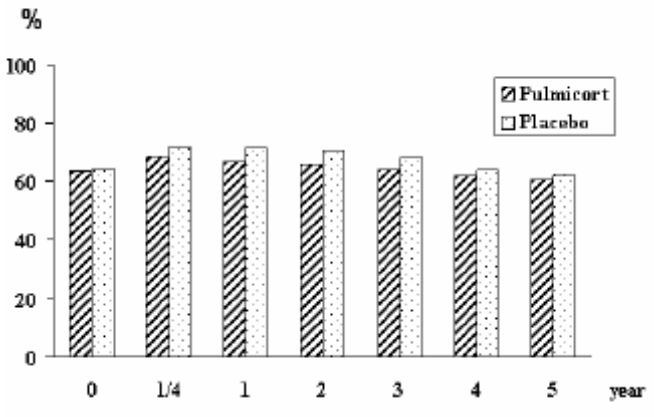
Co-Rapporteur's comment: This is a large-scale long term treatment study (double blind 3 yrs, open 2 yrs) which gives valuable safety information.

In children aged < 11 years at randomisation, 3-year growth in the Pulmicort group was statistically significantly (p<0.001) retarded by 1.34 cm (SE=0.17 cm). The treatment effect on growth was more pronounced during the first year (-0.58 cm) than during the second year (-0.43 cm) and third year (-0.33 cm).

Figure 10 **Patients on additional inhaled GCS[4] (including combinations with LABA)**



Patients on short-acting β_2-agonists[6]



Here the known effect of BUD on growth in children is observed as well.
This study is not exclusively a paediatric trial. Therefore the AE´s cannot always be allocated to the children population.

Study code: SD-004-726
Study Phase: III
Country: USA, south-east Asia
Study design: multi-centre**,** randomised, double-blind, placebo-controlled, 5 parallel groups
Primary objective: to compare the efficacy and safety of the new version of the Turbuhaler (M3) with the current US version of the Turbuhaler (M0-ESP) in asthmatic children and adolescence.
Study and control drugs: BUD new Turbuhaler 360 mcg BID or 180 mcg once daily (OD); BUD old Turbuhaler 400 mcg BID or 200 mcg OD; PLAC
Duration: 12 weeks (11/02-09/04)

Primary endpoints: change of FEV1 during treatment
No. of randomised patients: N=516
Mean age: 11.6 months (6-17 months)
Main inclusion criteria: Paediatric patients diagnosed with asthma for at least 3 months. Asthma diagnosed by airflow limitation (FEV1 ≥ 75% ≤ 90% predicted for the 6-11- years old; ≥ 60% ≤ 90% predicted for the 11-17 years old) and positive reversibility test (FEV1 increase ≥ 12% post bronchodilatator). They also had to be steroid-naïve or should not have used ICS > 30 days.
Results:
Efficacy: With regard to FEV1 change from baseline both Inhaler showed statistically significant increase compared with placebo in all dose regimes. Dose related trends in FEV1 were observed between the low and the high dose treatment groups for both BUD products. Similar effects were seen in children and adolescence. In asthma symptom score and use of rescue medication placebo and active treatment had similar effects.
Safety: The overall incidence of AE´s were low and similar between all treatment groups(with a slightly higher number in the once a day dosing). There were 3 SAE´s reported but none of them were classified as study related.

Preferred term[b]	Treatment group, n (%) of subjects				
	PULMICORT TURBUHALER M3 360 µg bid (n=96)	PULMICORT TURBUHALER M0-ESP 400 µg bid (n=102)	PULMICORT TURBUHALER M3 180 µg qd (n=108)	PULMICORT TURBUHALER M0-ESP 200 µg qd (n=104)	Placebo[c] (n=106)
Total	44 (45.8)	49 (48.0)	57 (52.8)	53 (51.0)	58 (54.7)
Headache	5 (5.2)	6 (5.9)	9 (8.3)	13 (12.5)	7 (6.6)
Nasopharyngitis	10 (10.4)	8 (7.8)	6 (5.6)	5 (4.8)	11 (10.4)
Pharyngolaryngeal pain	6 (6.3)	5 (4.9)	7 (6.5)	4 (3.8)	10 (9.4)
Pyrexia	6 (6.3)	5 (4.9)	6 (5.6)	2 (1.9)	8 (7.5)
Upper respiratory tract infection	2 (2.1)	7 (6.9)	5 (4.6)	7 (6.7)	5 (4.7)
Cough	6 (6.3)	8 (7.8)	6 (5.6)	1 (1.0)	4 (3.8)
Asthma	2 (2.1)	3 (2.9)	3 (2.8)	2 (1.9)	6 (5.7)
Nasal congestion	4 (4.2)	5 (4.9)	3 (2.8)	2 (1.9)	0
Pharyngitis	4 (4.2)	4 (3.9)	1 (0.9)	1 (1.0)	2 (1.9)
Abdominal pain, upper	1 (1.0)	2 (2.0)	1 (0.9)	6 (5.8)	2 (1.9)
Sinusitis	1 (1.0)	2 (2.0)	4 (3.7)	1 (1.0)	4 (3.8)
Diarrhea	3 (3.1)	1 (1.0)	4 (3.7)	2 (1.9)	1 (0.9)
Allergic rhinitis	4 (4.2)	2 (2.0)	2 (1.9)	2 (1.9)	1 (0.9)
Epistaxis	2 (2.1)	1 (1.0)	1 (0.9)	1 (1.0)	5 (4.7)
Otitis media	3 (3.1)	1 (1.0)	2 (1.9)	0	1 (0.9)
Skin laceration	3 (3.1)	0	1 (0.9)	1 (1.0)	2 (1.9)
Gastroenteritis, viral	3 (3.1)	0	1 (0.9)	1 (1.0)	0
Neck pain	0	0	0	1 (1.0)	4 (3.8)

[a] Occurring in ≥3% of subjects in any treatment group.

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[b] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.
[c] All placebo groups combined.

Rapporteur's comment: This was a well created new study that shows the comparability of the two inhalers. PK-results lead to the conclusion of a more homogenous treatment with the new inhaler.
However, it remains unclear, why a benefit is only seen in spirometry but not in symptomatic and clinical aspects.

Co-Rapporteur's comment: This was a study which compared different versions of the Turbohaler, the results are not of particular interest for this procedure.

III. ASSESSMENT OF REQUESTED SUPPLEMENTARY INFORMATION

Q1.): (RAPP) In the German SPC dosing regime is divided for "adults and adolescents" and "children under 12 years of age". Because there are no studies submitted for children under 4 years of age and the number of infants, toddlers and preschool-children is so limited that no general conclusion can be made for this age group, the MAH should comment on how a right inhaler handling in the very young can be ensured and should discuss to restrict the use to children ≥5 years of age.

APPLICANT´S RESPONSE:

Patients aged 5 and older are generally considered to be able to use dry powder inhalers properly. There are studies indicating that even children under 5 years of age can generate sufficient inspiratory flow rates with the Turbuhaler device for effective drug delivery (Pedersen et al 1990), and that children over the age of 3 years benefit from training in the use of Turbuhaler (Agertoft and Pedersen 1998). However, due to the limited data for the youngest children, we agree to restrict the use of Pulmicort Turbuhaler to children 5 years of age and older.

To assist in ensuring correct use, the patient information leaflet already includes detailed instructions for use of the device. As noted in the German SmPC, it is important to ensure that the patients receive detailed instructions for correct use, and children should always have adult supervision when using the device.

Rapporteurs' comment: Issue resolved

Q2) (Rapporteur/Co-Rapporteur)

The MAH should discuss a harmonisation of the SPC and PIL throughout Europe in view of the paediatric information.

APPLICANT´S RESPONSE:

For Pulmicort Nebuliser Suspension and Pulmicort Turbuhaler, AstraZeneca has obtained national approvals in all Member States in Europe. The "EU work sharing project assessment of paediatric data of existing products" is an initiative from the Health Authorities in Europe and the intention for this initiative is not to be a harmonisation process for the SmPC and PIL throughout Europe. This has been discussed at EMEA with participants from MEB and EFPIA (meeting report MEB, EFPIA). It is the opinion of AstraZeneca that the current national SmPCs are adequate to ensure safety and efficacy for the patients, therefore no harmonisation of the SmPCs and PILs throughout Europe is deemed necessary. In addition, post-marketing surveillance confirms the safe use of the product with the current label.

Rapporteurs' comment: The Rapporteur acknowledge that the aim of the paediatric work sharing is not to harmonise the SPC and PIL as a whole but a harmonisation of the paediatric data throughout Europe taking into account the national Marketing authorisations should be possible and be achieved. A harmonised SPC-proposal would be helpful.

<V.1.4 Clinical safety>

One point should be mentioned, that safety aspects of ICS have been evaluated by the PhVWP recently. Main results are wording changes/additions in SPC points 4.2, 4.4, 4.8.
All aspects were adequately transformed in the German SPC but if and how these points are considered in the other European countries is not known and should therefore be checked by each country themselves.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rapporteur's and Co-Rapporteur's conclusion: *The MAH submitted altogether 9 studies of BUD via Turbuhaler in the therapy of persistent asthma in children those where either requested by the FDA or not yet submitted in all European countries. The studies enrolled altogether 4963 patients aged 4 to 17 years. But the contingent of 4 years old children is so limited that they must be regarded as single cases. Therefore the Rapporteur suggested limiting the use of Pulmicort Turbohaler to children of 5 years of age and over in those countries having lower age limits. Though most of these studies are not completely in accordance with the Note for guidance on the clinical investigation of medicinal products in the treatment of asthma, overall a positive benefit-risk-relation can be concluded for BUD Turbuhaler and that was not the primary aim for the MAH to collect just these trials. For BUD Turbuhaler is a widespread use product even in the paediatric population the goal of this bundle of trials was to answer special questions regarding the product being used in paediatrics, e.g. is the once a day dosing comparable to the multiple dosing, is there an effect on growth, is the new and old inhaler comparable. The answer is yes.*

No further comments requesting changes were received from the CMS. Therefore this report is considered to be final.
It is suggested that these amendments should be implemented in the countries where the respective wordings have not already been included in the SPCs using variation procedures.

PROPOSED CHANGES IN THE SPC

Section 4.2 If no lower age limit is specified, the lower age limit should be restricted to 5 years, if appropriate.

Section 4.4 The following wording agreed by the German PhVWP should be included; "Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is

important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained."