AstraZeneca

Clinical Study Report

Drug substance:	Budesonide
Document No.:	01
Edition No.:	
Study code:	SD-004-0111 (D5254C00111)
Date:	**9 December 2004**

START - Inhaled Steroid Treatment As Regular Therapy in early asthma A study of the effect of early intervention with long-term inhaled budesonide (Pulmicort Turbuhaler ®) in newly diagnosed asthma (3 year doubl-blind + 2 year open label follow-up).

Study dates:	First subject enrolled: 19 September 1996 Last subject completed: 8 Februray 2003
Phase of development:	Phase IV
International Coordinating Investigator:	There was no international co-ordinating investigator in this study. However, there was a Steering Committee.

This study was performed in compliance with Good Clinical Practice.

AstraZeneca

Drug product:	PULMICORT TURBUHALER	**SYNOPSIS**	
Drug substance(s):	Budesonide		
Document No.:			
Edition No.:			
Study code:	SD-004-0111		
Date:	9 December 2004		

START - Inhaled Steroid Treatment As Regular Therapy in early asthma A study of the effect of early intervention with long-term inhaled budesonide (Pulmicort Turbuhaler ®) in newly diagnosed asthma (3 year doubl-blind + 2 year open label follow-up).

International coordinating investigator:
There was no international co-ordinating investigator in this study. However, there was a Steering Committee.

Study center
This study was conducted in 32 countries at 500 centres.

Table S2 No. of centres in each country/region.

Country	No. of centres	Country	No. of centres	Country	No. of centres
Argentina	9	Greece	17	Poland	21
Australia	4	Hungary	15	Portugal	22
Austria	9	Indonesia	9	Singapore	5
Belgium	17	Israel	16	South Africa	18
Canada	7	Italy	14	Spain	34
China	45	Korea	6	Sweden	12
Czech Republic	20	Malaysia	8	Taiwan	6

Country	No. of centres	Country	No. of centres	Country	No. of centres
Denmark	8	Malta	3	Thailand	13
Finland	14	Mexico	22	United Kingdom	5
France	12	Norway	11	USA	51[1]
Germany	36	Philippines	11	TOTAL	500[1]

[a] One centre (828) enrolled 10 patients but they were never randomized. 499 centres randomized patients.

Publications

Pauwels R et al. The Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study: Rationale and Design. Control Clin Trials 2001; 22:405-419.

Sullivan SD et al. Design and analytical considerations in determining the cost-effectiveness of early intervention in asthma from a multinational clinical trial. Control Clin Trials 2001; 22:420-437.

Pauwels R et al. Early intervention with budesonide in mild persistent asthma: a randomized, double-blind trial. The Lancet 2003; 361:1071-1076.

Sullivan SD et al. Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma. Journal of Allergy Clinical Immunology 2003; 112:1229-36.

STUDY DATES

Final protocol 1995-12-08; Amendment 1 1996-07-09; Amendment 2 1999-05-26; Administrative Change 1 2002-05-28

Clean File and database locked, Part A: 20 April, 2001
Clean File and database locked, Part B: 10 April, 2003

Study dates

First subject enrolled 19 September 1996
Last subject completed 8 Februray 2003

PHASE OF DEVELOPMENT

Clinical pharmacology (I)

Therapeutic exploratory (II)

Therapeutic confirmatory (III)

Therapeutic use (IV)

OBJECTIVES

The primary objective of START was to evaluate if early intervention with Pulmicort affects the evolution of newly-diagnosed asthma.

The first primary variable for the first 3 years of the double-blind phase was the time to the first severe asthma-related event (SARE). The second primary variable for the entire 5 years was the change in post-bronchodilator FEV_1 % predicted over time compared with baseline.

STUDY DESIGN

The study was of a multi-centre, multi-national, 3-year double-blind, randomized and parallel-group design, with a 2-year open-label follow-up. The total time of the entire study was 5 years.

TARGET PATIENT POPULATION AND SAMPLE SIZE

Patients with newly diagnosed, mild, persistent asthma were recruited from 32 countries. Over 7200 patients, male and female 6-60 years, who fulfilled all of the inclusion and none of the exclusion criteria were randomized.

Important inclusion and exclusion criteria:

Table S3 Important inclusion and exclusion criterias.

Important inclusion criteria:	Important exclusion criteria:
Ages 6 to 60 years.	Asthma symptoms or treatment for more than 2 years.
Mild persistent asthma, diagnosed preferably within 1 year, but not more than 2 years, prior to visit 1.	Delayed introduction of inhaled GCS judged inappropriate.
Able to use Turbuhaler.	More than 30 days of GCS treatment or more than one depot injection per year.
Written informed consent.	Pre-bronchodilator FEV_1 < 60% predicted. Post-bronchodilator FEV_1 > 80% predicted.
	Concomitant serious disease.

Table S4 Diagnostic Criteria for Mild Persistent Asthma[a]

Symptoms	Reversible Airway Obstruction
One of the following at least once a week, but not as often as every day, during the 3 months prior to entry to the study. - wheeze - cough - dyspnea - chest tightening	One of the following present at the first clinic visit or demonstrated from historical data: - An increase in FEV_1 of more than 12% compared with baseline after inhalation of a short-acting bronchodilator. - Fall in FEV_1 15% from baseline on exercise testing.

- nocturnal waking due to any of the above.
Cough as an isolated symptom can be present every day.

- PEF variations: for a 14-day period, discard the first 3 days' values, and calculate PEF variability as shown below[b] . PEF variability should be >15%.

FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow.
[a]Both symptoms and reversible obstruction must be present for the diagnosis to be made. Bronchial hyperresponsiveness (unless exercise-induced) will not be accepted as an alternative to any of these criteria.
[b]Daily PEF variations is calculated as follows:

$$PEF_{Var} = \frac{(A1 + A2) - (B1 + B2)}{(A1 + A2)} \times 100$$

where A1 = highest PEF; A2 = second highest PEF; B1 = lowest PEF; B2 = second lowest PEF

INVESTIGATIONAL PRODUCT AND COMPARATOR(S): DOSAGE, MODE OF ADMINISTRATION AND BATCH NUMBERS

Investigational drug:
Pulmicort Turbuhaler® 400 µg/dose, 200 doses (budesonide powder for inhalation, Astra Pharmaceutical Production, Södertälje, Sweden).
Pulmicort Turbuhaler 200 µg/dose, 200 doses (budesonide powder for inhalation, Astra Pharmaceutical Production, Södertälje, Sweden).

Reference drug:
Placebo Pulmicort Turbuhaler 200 µg/dose, 200 doses (lactose powder for inhalation, Astra Pharmaceutical Production, Södertälje, Sweden).

Batch-numbers:

Table S5 Investigational products - all countries except USA

Pulmicort TBH 200		**Pulmicort TBH 400**	**PLACEBO Pulmicort THB 200**	**Bricanyl TBH 0.5**
Version	**Batch number**	**Batch number**	**Batch number**	**Batch number**
M2	XD 779	XD 412	VA 323*	XC 813
M2	XM 866	XM 476	VI 326*	XE 835
M2	YG 923	YG 526	XD 24	XG 862
M2	ZC 988	YM 560	XM 25	XM 911
M2	ZF 1014	ZC 575	YD 26	YA 916
M2	AA 1072	ZF 600	YG 27	ZB 1021
M2	AD 1102	AA 640	ZC 28	ZE 1046
M2	AI 1144	AD 651	ZD 29	ZG 1058
M2	BC 1175	AK 669	ZF 30	ZH 1061

Pulmicort TBH 200		**Pulmicort TBH 400**	**PLACEBO Pulmicort THB 200**	**Bricanyl TBH 0.5**
Version	**Batch number**	**Batch number**	**Batch number**	**Batch number**
M2	BH 1198	BC 684	AA 31	ZK 1079
M2	CD 1238	BI 707	AD 32	ZM 1087
		CD 723	AI 33	AC 1106
				AC 1107
				AL 1138
				352520F
				BC 1161
				BH 1170
				CB 1177
				CE 1183
				CF 1185

[a] *only for demostration

Table S6 Investigational products - USA

START - USA

Pulmicort TBH 200 USA		Pulmicort TBH 400 USA	PLACEBO Pulmicort THB 200
Version	Batchnumber	Batchnumber	Batchnumber
M0	DYL 122	XH 109**	XH 11**
M0	XH 83**	YB 122***	YB 12***
M0	YC 101***	YK 130	YI 13
M0	ZE 149	ZI 132	ZF 14
M0	ZE 150	ZI 133	ZL 15
M0	ZI 168	ZI 134	AH 16
M0	AE 178	ZI 135	
M0	AF 180	ZI 136	
M0	AF 181	BE 152	
M0	AF 182	DAH 120	
M0	AF 185	BH 156	
M0	AF 186		
M0	BC 200		
M0	BI 206		

M0	CD 208
M0-ESP	CE 1433
M0-ESP	CH 1497

[a] **ordered for START-USA but never sent
[b] ***sent to USA directly from Södertälje

DURATION OF TREATMENT

Treatment with inhaled Pulmicort (budesonide) or Placebo for 3 years followed by Pulmicort for 2 years. Total time of the study was five years.

Part A: 3-year double-blind phase
Part B: 2-year open label phase

CRITERIA FOR EVALUATION (MAIN VARIABLES)

EFFICACY

- Primary variable:

  – Severe Asthma-Related Event (SARE), with the primary endpoint time to the first SARE in the double-blind phase.

  – Post-bronchodilator FEV_1 % of predicted normal, with the primary endpoint change from baseline to the end of the open-label phase

- Secondary variables:

  – Pre-bronchodilator FEV_1 %, post-bronchodilator FVC%, post-bronchodilator FEV_1 /FVC%, additional inhaled or systemic GCS, oral steroids courses, asthma-related symptoms, growth in children.
  For Health Economics evaluation: asthma-related events and health care utilization, and Symptom-Free Days (SFDs).

SAFETY

Adverse events (AEs), Serious Adverse Events (SAEs), Discontinuations due to Adverse Events (DAEs). Other observations related to safety. Pregnancy data.

STATISTICAL METHODS

Incidence of severe asthma-related events (SAREs), as well as other rates and proportions, is analysed using chi-2 methods. Time to the first SARE, and time to the first addition of inhaled or systemic glucocorticosteroids, is analysed using proportional hazards regression. Change from baseline in post- and pre-bronchodilator FEV_1 % predicted, and percent symptom-free days, is analysed using analysis of variance and mixed models. Growth in children is analysed using mixed models.

PATIENT POPULATION

Table S7 Patient population and disposition

		Pulmicort	Placebo	Total
Population				
Randomized		3642	3599	7241
Demographic characteristics				
Sex (n and % of patients)	Male (SD)	1648 (46)	1643 (46)	3291 (46)
	Female (SD)	1949 (54)	1925 (54)	3874 (54)
Age (years)	Mean (SD)	23.68 (14.57)	24.26 (14.84)	23.97 (14.71)
	Range	4 to 65	5 to 66	4 to 66
Race (n and % of patients)	Caucasian (SD)	2351 (65)	2310 (65)	4661 (65)
	Black (SD)	50 (1.4)	62 (1.7)	112 (1.5)
	Oriental (SD)	998 (28)	997 (28)	1995 (28)
	Other (SD)	198 (5.5)	199 (5.6)	397 (5.5)
Baseline characteristics				
Number of hospitalizations/emergency treatments[1]				0.26 (0.89)
Mean	Pre-FEV_1% pred. (SD) Litre (SD)	86.34 (13.9) 2.32 (0.88)	86.56 (13.9) 2.35 (0.90)	86.45 (13.91) 2.34 (0.89)
	Post-FEV_1% pred. (SD) Litre (SD)	96.22 (13.1) 2.58 (0.92)	96.4 (13.3) 2.61 (0.96)	96.31 (13.2) 2.6 (0.94)
Disposition				
N (%) of patients who	completed	2395	2317	4712
	discontinued	1247	1282	2529
N analysed for safety		3630	3591	7221
N analysed for efficacy (ITT)		3597	3568	7165

[a] during the past 12 months due to asthma

The overall number of discontinuations, and number of patients who discontinued study treatment due to AE, was similar between the treatment groups. Overall, the two treatment groups were comparable for demographic characteristics and had similar baseline lung function.

EFFICACY RESULTS

Figure S1 Summary of additional asthma medication. Difference between Pulmicort and Placebo.

	Double-blind phase	Open-label phase
Inhaled corticosteroids	p<0.001	p<0.001
Oral/systemic corticosteroids	p=0.009	NS (p=0.79)
Short-acting β_2-agonists	p<0.001	NS (p=0.17)
Long-acting β_2-agonists	p<0.001	p<0.001
Xanthines	p=0.02	NS (p=1.00)
Cromones	NS (p=0.28)	p=0.003
Leukotriene modifiers	NS (p=0.78)	NS (p=0.90)
Other asthma medications	NS (p=0.25)	NS (p=1.00)

Patients on Placebo received more and earlier additional inhaled and oral glucocorticosteroids, and also more additional non-steroidal asthma medication, than did those on Pulmicort.

Figure S2 First severe asthma-related event

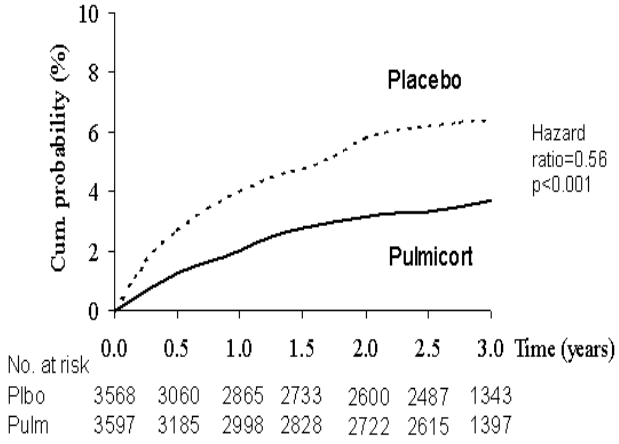


Figure S3 SAREs

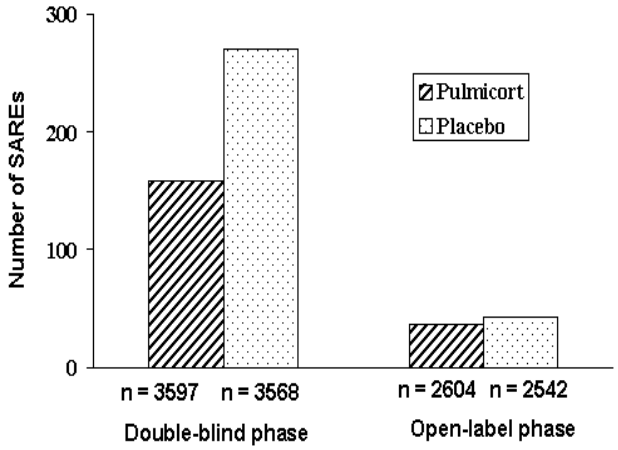


Figure S4 Post-bronchodilator FEV_1 % predicted. All (completers).

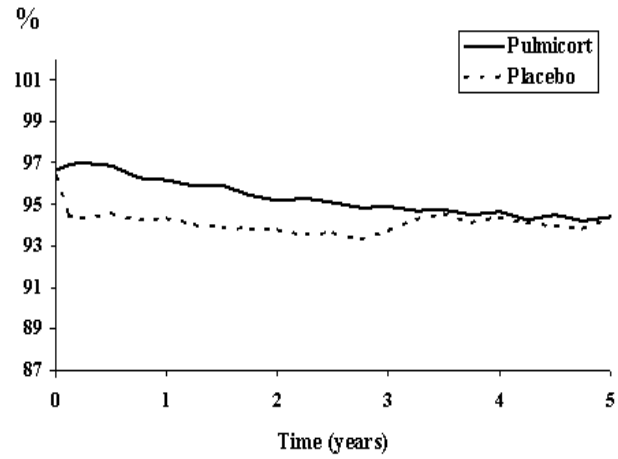


Figure S5 Post-bronchodilator FEV_1 % predicted. 5-year change from baseline. Analysis of variance.

Overall treatment effect: p=0.62

Demographic Factor	Main effect	Differential effect (Pulmicort-Placebo)
Sex	p<0.001	p=0.93
Age	p<0.001	p=0.25
Smoking habits	p<0.001	p=0.46

Figure S6 Summary of symptoms. Difference between Pulmicort and Placebo.

	Double-blind phase	Open-label phase
Restrictions in normal activities	p<0.001	NS (p=0.51)
Sleeping problems	p<0.001	NS (p=0.62)
Asthma symptoms	p<0.001	NS (p=0.14)

In the 3-year double-blind phase, the risk of a Severe Asthma-Related Event (SARE) was nearly halved in the Pulmicort group compared to the Placebo group, but no difference in SARE incidence was seen in the open-label phase.

A positive treatment effect was seen in both post- and pre-bronchodilator FEV_1 % predicted at the end of the double-blind phase (after 3 years), but in the open-label phase a rapid catch-up in spirometric variables occurred in the Placebo group, and so there was no difference in spirometric variables at the end of the study (after 5 years).

There were more asthma-related symptoms in the Placebo group (compared to the Pulmicort group) in the double-blind phase, but in the open-label phase no differences were seen.

There was more and earlier use of additional inhaled and systemic glucocorticosteroids, long-acting and short-acting β_2-agonists and xanthines in the Placebo group (compared to the Pulmicort group) in the double-blind phase.

HEALTH ECONOMICS RESULTS

Table S8 3-year resource consumption by age and treatment group

Units, mean (SE)

	Pulmicort (n=3597)				**Placebo (n=3568)**				
Item	**—10 years**	**11-17 years**	**18- years**	**Overall (all ages)**	**—10 years**	**11-17 years**	**18- years**	**Overall (all ages)**	**Overall Difference* [% Difference]**
Hospital days	0.2	0.12	0.17	0.17 (0.03)	0.39	0.44	0.66	0.55 -0.12	-0.38§ (0.12) [-69%]
Emergency visits	0.03	0.01	0.03	0.03 (0.01)	0.05	0.06	0.11	0.09 -0.02	-0.06† (0.03) [-67%]

Units, mean (SE)

	Pulmicort (n=3597)				Placebo (n=3568)				
Item	**—10 years**	**11-17 years**	**18-years**	**Overall (all ages)**	**—10 years**	**11-17 years**	**18-years**	**Overall (all ages)**	**Overall Difference* [% Difference]**
Physician visits	1.73	1.02	1.17	1.30 (0.05)	2.53	1.33	1.99	2.03 -0.07	-0.73§ (0.09) [-36%]
Nurse visits	0.06	0.09	0.08	0.08 (0.01)	0.17	0.11	0.12	0.13 -0.02	-0.05‡ (0.02) [-38%]
Telephone contacts	0.57	0.47	0.34	0.42 (0.03)	0.89	0.47	0.57	0.64 -0.04	-0.22§ (0.05) [-34%]
Work and school days lost	4.3	3.41	2.63	3.22 (0.22)	5.67	3.97	5.27	5.16 -0.35	-1.94§ (0.42) [-37%]
Caregiver work days lost	1.45	0.45	0.09	0.53 (0.08)	2.19	0.46	0.05	0.71 -0.1	-0.18 (0.13) [-25%]

[a] *Difference = Pulmicort Placebo; % Difference = 100 ´ (Pulmicort - Placebo)/Placebo. Statistical test of difference: Stratified Wilcoxon test for hospital days and stratified z-test for other items. Tests are two-tailed.

[b] †Significant at P<0.05; ‡Significant at p<0.01; §Significant at p<0.001.

Figure S7 Percent symptom-free days

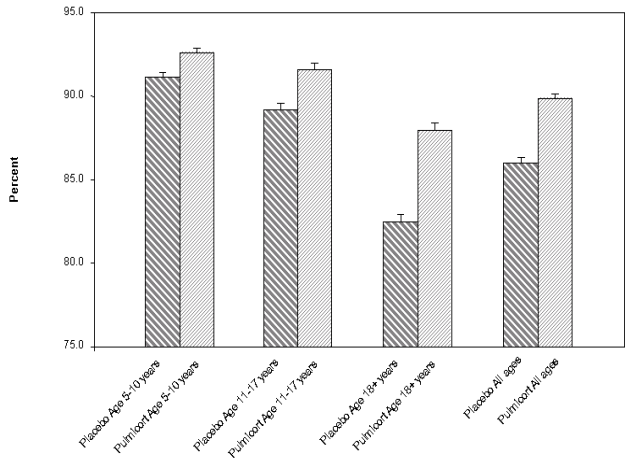
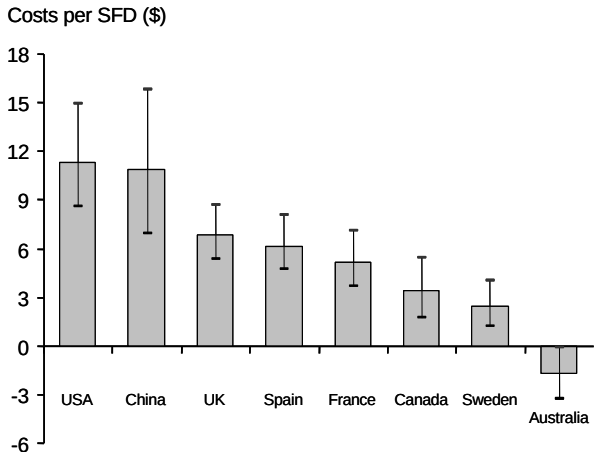


Figure S8 PPP-adjusted ICERs for each countries' set of relative prices. From the healthcare payer perspective, 3-year results.



Early intervention with Pulmicort has been shown to be an effective therapy, which significantly improves SFDs (Symptom-Free Days), and reduces hospitalisations, emergency room visits, physician office visits, oral steroid and other concomitant medication use and costs. For children, early intervention is a cost-saving strategy.

The results after 5 full years confirm the cost-effectiveness of initiating Pulmicort early. Indeed, these results are even more in favour of Pulmicort as the net difference in costs is further reduced and the benefits in SFDs enhanced.

SAFETY RESULTS

Table S9 Number (%) of patients who had an adverse event in any category, and total number of adverse events during Part A

Category of adverse event	Pulmicort (N=3630)	Placebo (N=3591)	Total (N=7221)
Number (%) of patients who had an adverse event in each category [1]			
Any adverse events	2774 (77%)	2738 (76%)	5512 (76%)
Deaths	3[2]	8	11[2]
Any serious adverse events	406 (11%)	497 (14%)	903 (13%)
Deaths and discontinuations of study treatment due to adverse event (non-asthma)	46 (1.3%)	44 (1.2%)	90 (1.2%)
whereof deaths	3	7	10

Category of adverse event	Pulmicort (N=3630)	Placebo (N=3591)	Total (N=7221)
whereof non-fatal	43	37	80
Deaths and discontinuations of study treatment due to worsening of asthma	3	6	9
whereof deaths	0	1	1
Other significant adverse event	0	0	0
Total numbers of adverse events (number of symptoms reported)			
Any adverse events[3]	10828	10658	21486
Number of symptoms reported as serious adverse events including deaths	565	733	1298
whereof non-asthma	404	459	863
whereof asthma	161	274	435
Number of symptoms leading to death or discontinuation of study treatment	55	58	113
whereof non-asthma	52	51	103
whereof asthma	3	7[4]	10
Other significant adverse events	0	0	0

[a] Patients with multiple events in the same category are only counted once in that category. Patients with events in more than one category are counted in each of those categories.
[b] Excluding one post-study death
[c] Summarised as number of symptoms per preferred term
[d] One patient discontinued due to coughing, fatigue and asthma. This patient is counted as discontinued due to AE (non-asthma).

Table S10 Number (%) of patients who had an adverse event in any category, and total number of adverse events during Part B

Category of adverse event	Pulmicort (N=5150)
Number (%) of patients who had an adverse event in each category[1]	
Deaths	10[2]
Any serious adverse event	311 (6%)
Deaths and discontinuations of study treatment due to adverse event (non-asthma)	20 (0.4%)
whereof deaths	8

Category of adverse event	Pulmicort (N=5150)
Deaths and discontinuations of study treatment due to worsening of asthma	3
whereof deaths	2
Other significant adverse event	0
Total number of adverse events (number of symptoms reported)	
Number of symptoms reported as serious adverse events including deaths	434
whereof non-asthma	343
whereof asthma	91
Number of symptoms leading to death or discontinuation of study treatment	27
whereof non-asthma	24
whereof asthma	3
Other significant adverse events	0

[a] Patients with multiple events in the same category are only counted once in that category. Patients with events in more than one category are counted in each of those categories.
[b] Excluding one post-study death.

Table S11 Most frequently reported adverse events by preferred term, Part A. Number (%) of patients reporting at least one AE after first dose of investigational product

Preferred term	Pulmicort (N=3630)		Placebo (N=3591)		Total (N=7221)	
	N	(%)	N	(%)	N	(%)
Respiratory infection	1395	-38%	1372	-38%	2767	-38%
Rhinitis	860	-24%	788	-22%	1648	-23%
Pharyngitis	772	-21%	774	-21%	1546	-21%
Bronchitis	576	-16%	618	-17%	1194	-17%
Infection viral	544	-15%	502	-14%	1046	-14%
Sinusitis	341	-9%	327	-9%	668	-9%
Headache	310	-9%	297	-8%	607	-8%
Accident and/or injury	254	-7%	265	-7%	519	-7%
Coughing	264	-7%	219	-6%	483	-7%
Conjunctivitis	218	-6%	210	-6%	428	-6%

Table S12 Number of deaths, SAEs and DAEs from Parts A and B

	Pulmicort Part A	Placebo Part A	Pulmicort Part B	All patients Part A + B
Number of million treatment days	3.3	3.2	3.6	10.1
Serious adverse event reports[1]	537	694	392	1623
leading to death	4	8	11	23
not leading to death	533	686	381	1400
related to asthma[2]	161	273	90	524
not related to asthma	376	421	302	1299
Discontinuations due to adverse events/asthma deterioration	49	50	23	122
not related to asthma	46	44	20	110
related to asthma	3	6	3	12

[a] Including post-study deaths
[b] Not identical to the events reported as SAREs. This entry summarises all SAEs by Preferred term =”Asthma aggravated” or “Bronchospasm”.

Table S13 Overview of pregnancies, entire study

	Pulmicort (Part A+B)	Placebo	Total
No of females aged 15 - 50 at randomisation	1250	1223	2473
Total number of pregnancies with known outcome	196	117	313
Total number of pregnancies with unknown outcome	5	1	6
Outcome favourable	158 (81%)	90 (77%)	258
Outcome non-favourable	38 (19%)	27 (23%)	65

Table S14 Overview of pregnancies with outcome = non-favourable (entire study)

	Pulmicort (Part A+B)	Placebo	Total
Miscarriage	23 (12%)	11 (9%)	34
Congenital abnormality	3 (1.5%)	4 (3.4%)	7
Extrauterine	4 (2.0%)	3 (2.6%)	7
Induced abortion	6 (3.1%)	6 (5.1%)	12

	Pulmicort (Part A+B)	Placebo	Total
Other outcome	2 (1.0%)	3 (2.6%)	5

The number of SAEs and discontinuations due to AEs was low during the open-label treatment period (Part B) and the partition of such events between patients treated with Pulmicort and Placebo, respectively, during Part A revealed no findings of importance.

The overall frequency of patients reporting AEs during Part A was similar in the different sex, age and race groups. The only AEs evidently more common in the Pulmicort group than in the Placebo group were local adverse events such as cough, dysphonia and candida infection in the mouth, well in line with the established risk profile of inhaled budesonide.

No clinically important differences were observed between Pulmicort and Placebo during Part A in the incidence of potential systemic effects such as adrenal suppression, cataract formation/glaucoma, osteoporosis, long-term effects on growth and skin bruising.

In this study, similar pregnancy outcomes were observed in all treatment groups, with a low incidence of congenital abnormalities, miscarriage, extrauterine pregnancies and induced abortion.

DATE OF THE REPORT

9 December 2004