Of note, there was a statistically significant dose response ($p<0.01$) in urinary cortisol excretion showing that higher doses gave reduced urinary free cortisol. The two highest doses of budesonide nebulizing suspension (2.0 and 4.0 mg/day) statistically significantly reduced (43-52%) the excretion of 24 hour urinary free cortisol (creatinine normalized) compared with the run-in period.

Table 8.5.2.4.2. Standardized 24-hour Urinary Excretion of Free Cortisol.
[88:49, 58-60, 64]

Study Period	N[1]	Urinary Excretion of Free Cortisol[2] Mean+SD (Range)
Run-in	10	14.71+5.03 ([redacted]
0.5 mg BID budesonide nebulizing suspension	17	9.95+3.65 ([redacted]
1.0 mg BID budesonide nebulizing suspension	16	8.41+3.59 ([redacted]
2.0 mg BID budesonide nebulizing suspension	18	7.04+4.00*, a, b ([redacted]

1 The data of urinary excretion of free cortisol were not available for all patients at all time points due to missing samples or aberrant samples as revealed by the creatinine values.
2 Urinary excretion of free cortisol = (Urine cortisol in nmol/Urine creatinine in mmol) x 10^6.
* $p<0.05$ vs. Run-in.
a $p<0.001$ vs. 0.5 mg BID budesonide nebulizing suspension.
b $p<0.05$ vs. 1.0 mg BID budesonide nebulizing suspension.

Reviewer's Comments: 1. The 0.5 mg BID budesonide nebulizing suspension also numerically reduced (32%) the excretion of 24 hour urinary free cortisol (creatinine normalized) indicating a measurable systemic effect. 2. There were no washout periods between treatment periods. It's possible that a HPA-axis suppression by a higher dose regimen could be carried over to the following treatment period. However, the influence of such a carry-over effect on the mean urinary excretion of free cortisol should have been minimized by randomization.

8.5.3 *Study 04-2151: An Attempt to Find Clinically Equivalent Doses of Budesonide Administered from a Metered Dose Inhaler or as a Suspension for Nebulization.*

8.5.3.1 Objectives

[105: 28]
To estimate clinically equivalent doses between budesonide nebulizing suspension and budesonide pMDI connected to a spacer ([redacted] in adult patients with moderately severe asthma.

8.5.3.1.1 Efficacy Variables

[105:35]
Physician's Recordings:
- Spirometry (FEV_1 and PEF).

Patient's Recordings:
- Morning and evening PEFs.

- Five subjective variables (yes/no scores): cough, breathlessness, wheezing, night asthma symptoms, and normal activities.
- Use of β_2-agonist.

8.5.3.1.2 Safety Variables

[105:35-6]

- Reported adverse events.
- Morning plasma basal cortisol levels in a subset (n=10) of patients.
- Throat swab if any sign of clinical candidiasis.

8.5.3.2 Design

[105:27]

This was a randomized, double-blind, positive-controlled, double-dummy, cross-over study of 1.0 mg and 4.0 mg BID budesonide nebulizing suspension compared to 0.8 mg BID budesonide pMDI connected to a [redacted] in adult patients with moderately severe asthma. Each treatment period was 4 weeks. Budesonide nebulizing suspension was delivered via [redacted] nebulizer connected to a [redacted] compressor.

8.5.3.3 Study Population

[105:29, 37]

- Twenty-six asthmatic patients (9 males and 17 females) aged 27-62 years (mean = 45 years) requiring daily treatment with a combination of inhaled β_2-agonist and inhaled steroids, but still not adequately controlled (one or more parameters of PFT $\leq$80% of predicted). The mean initial FEV_1 was 1.96$\pm$0.57 (SD) L. Twenty-one patients completed the study.
- The first patient was enrolled into the study in March, 1987. The last patient completed the study in November, 1987.

8.5.3.4 Results

8.5.3.4.1 Efficacy Results

[105:38-44, 58-9]

Compared to 0.8 mg BID budesonide pMDI, the 1 mg BID or 4 mg BID budesonide nebulizing suspension was associated with significant improvements in breathlessness, wheezing, and evening PEF. In addition, there were significant improvements in the morning PEF, night asthma symptoms, and use of β_2-agonist in the 4 mg BID budesonide nebulizing suspension group compared to budesonide pMDI. Between treatment groups, there was no significant difference in PEF or FEV_1 measured by spirometry.

Table 8.5.3.4.1: Efficacy Variables. [105:58-9]

Efficacy variable	Budesonide nebulizing suspension[1]		Budesonide pMDI[1]
	1 mg BID	4 mg BID	0.8 mg BID
Patient's recordings			
Subject variables[2]			
Cough	0.31±0.09 (23)	0.16±0.07 (22)	0.32±0.09 (21)
Breathlessness	0.27±0.08* (23)	0.21±0.06* (22)	0.43±0.09 (21)
Wheeze	0.25±0.08* (23)	0.23±0.08* (22)	0.39±0.09 (21)
Night asthma symptoms	0.20±0.07 (23)	0.10±0.05* (22)	0.25±0.08 (21)
Normal activity	0.81±0.08 (23)	0.87±0.06 (22)	0.84±0.07 (21)
Use of β_2-agonist			
# of puffs/day	7.6±0.8 (23)	7.1±1.0* (21)	8.8±1.1 (21)
PEF (L/min)			
Morning	331±22 (23)	349±21* (22)	329±22 (21)
Evening	371±23* (23)	386±22* (22)	363±22 (21)
Physician's recordings			
PEF (L/min)	386±30 (13)	354±30 (12)	383±47 (9)
FEV_1 (% of predicted)	77±6 (13)	71±6 (12)	72±9 (9)

[1] Mean+SEM (n).
[2] No = 0; yes = 1.
* $p \leq 0.05$ compared to pMDI.

8.5.3.4.2 *Safety Results*

[105:10-8, 45-7, 60]

There were no deaths reported during the study. There was no apparent differences between the treatment groups in the numbers or types of AEs reported except that moniliasis was more frequent (6/22) and respiratory infection less frequent (2/22) in 4.0 mg BID budesonide nebulizing suspension group compared to 1.0 mg BID budesonide nebulizing suspension group (3/24 and 7/24, respectively) or 0.8 mg BID budesonide pMDI group (2/23 and 8/23, respectively). There were 3 SAEs reported in 2 patients (cervix carcinoma in one patient receiving 1.0 mg BID budesonide nebulizing suspension; congenital malformation/neonatal asphyxia in a baby born by a patient receiving 0.8 mg BID budesonide pMDI during the first trimester of pregnancy). The causal relationship of cervix carcinoma was judged to be unlikely by the investigator. The causal relationship of congenital malformation/neonatal asphyxia was judged to be "cannot be classified" by the investigator.

Of note, the plasma cortisol level of the 4.0 mg BID Budesonide nebulizing suspension group was significantly lower than that of the 0.8 mg BID budesonide pMDI in a subset of 10 patients. Also, the plasma cortisol level of the 1.0 mg BID budesonide nebulizing suspension group was numerically lower than that of the 0.8 mg BID budesonide pMDI group although the difference was not statistically significant.

Table 8.5.3.4.2: Plasma Cortisol Levels.[1] [105:60]

	Budesonide nebulizing suspension		Budesonide pMDI
Plasma cortisol (nmol/L)	**1 mg BID**	**4 mg BID**	**0.8 mg BID**
Before treatment	446±55	369±36*	484±29
60 minutes after treatment	261±43	215±29	268±23
120 minutes after treatment	187±30	141±19*	202±17

[1] Mean+SEM (n=10).
* $p \leq 0.05$ compared to pMDI.

Reviewer's comments: Using the data from this study and the following study (04-2270), the sponsor claims that ' [redacted] *' in the proposed labeling. However, there was no placebo-control treatment period in this study. The observed improvements in some efficacy variables in the treatment groups could be due to placebo effects. In addition, the doses used and the increased adverse events observed, e.g., moniliasis, were not mentioned in the proposed labeling.*

8.5.4 Study 04-2270: Budesonide Nebulizing Suspension as an Oral Steroid Sparing Agent in Adult Patients with Chronic Asthma.

8.5.4.1 Objectives

[106:1, 10]

To assess the ability of 4.0 mg BID budesonide nebulizing suspension to replace oral steroid use by adult patients with chronic asthma.

8.5.4.1.1 Efficacy Variables

[106:1, 16-7]

Physician's Recordings:

- Spirometry (FEV_1 and FVC).

Patient's Recordings:

- Daily dose of oral steroids.
- Use of other asthma medications.
- Morning and evening PEFs.
- Morning and evening asthma symptoms (0-3 scores).

8.5.4.1.2 Safety Variables

[106:1, 17-9]

- Adverse events reported by the patient or observed by the investigator.
- Clinical chemistry, hematology, and urinalysis (including creatinine and cortisol levels).

8.5.4.2 Design

[106:11-2]

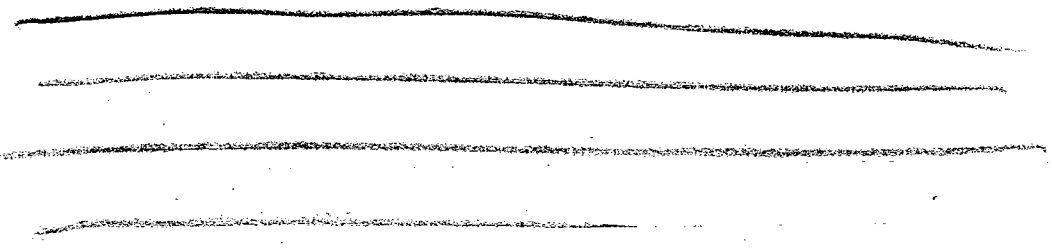
This was a randomized, double-blind, parallel-group study to assess the ability of 4.0 mg BID budesonide nebulizing suspension to replace oral steroid use by adult patients with oral steroid dependent asthma compared to 0.5 mg BID budesonide nebulizing suspension. Randomization was preceded by a 2-week run-in period during which 5.0 mg BID nebulized terbutaline was introduced. After randomization, budesonide nebulizing suspension replaced the usual inhaled corticosteroids. Prednisolone reduction was commenced after one week and step-wise reductions continued on a weekly basis. Patients returned to the clinic every 2 weeks until prednisolone was completely withdrawn, with the patient remaining stable for at least one week, or an exacerbation of asthma occurred.

8.5.4.3 Study Population

[106:12-3, 24-6]

- Thirty-nine asthmatic patients (18 males and 21 females) aged 27-75 years (mean = 48 years) requiring daily dose of at least 0.8 mg inhaled steroids and 7.5 mg oral prednisolone, and $FEV_1 \geq 50\%$ of predicted were randomized. Thirty-seven patients reached a study end-points.
- The first patient was enrolled into the study in November, 1990. The last patient completed the study in January, 1993.

8.5.4.4 Results



There were 3 SAEs (2 exacerbations of asthma and 1 cardiac ischemic event) reported in 3 patients receiving 4.0 mg BID budesonide nebulizing suspension. [106:40-1]

In the report of this study, the sponsor concluded that the study design employed in this study was faulty and, as a consequence, it was not possible to make definite conclusions about the efficacy and safety of 4.0 mg BID budesonide nebulizing suspension as an oral steroid sparing agent compared to 0.5 mg BID. The deficiencies of the study listed by the sponsor included the following: 1. A parallel placebo arm was not included in the study due to ethical limitations. 2. There were no assessments or existing evidence to demonstrate that the starting levels of oral corticosteroid were optimal for each individual patient. Therefore, patients could have been receiving higher doses of steroids than necessary, enabling dose reductions with no detriment in asthma symptoms. 3. The high dose of daily nebulized terbutaline (5 mg BID) may have masked the asthma symptoms during the reduction of oral corticosteroids. 4. The doses of oral corticosteroids were reduced weekly. This was possibly too short for many symptoms to appear. [106:2, 9]

Reviewer's comments: In view of the faulty design of the study, no statement in the labeling should be based on the data generated in this study. The study could have had a non-steroid conventional asthma therapy arm.

9. INTEGRATED SUMMARY OF EFFICACY (ISE)

9.1 Introduction

The purpose of this summary is to integrate into one document the efficacy results of studies of budesonide nebulizing suspension for the maintenance treatment of asthma as prophylactic therapy in children between the ages of ——— and eight years. The focus of this summary is on the effectiveness of budesonide nebulizing suspension demonstrated in three pivotal, randomized, double-blind, placebo-controlled, parallel-group studies conducted in the U.S. although synopses for 13 completed non-U.S. supportive studies were also provided by the sponsor in the ISE of NDA.

9.2 U.S. Pivotal Clinical Studies

9.2.1 Three Randomized, Controlled, Double-Blind, Pediatric Studies (04-3069, 04-3072, 04-3100)

9.2.1.1 Design Features and Numbers of Patients

[133:23-4, 36]

A total of 1,018 patients were randomized into the double-blind treatment phase of the three U.S. pivotal, double-blind, controlled, pediatric studies. Of these, 1,007 patients were evaluable for efficacy. Eleven randomized patients (one from Study 04-3069 and 10 from Study 04-3100) were excluded from the APT efficacy analyses because no efficacy measurements were taken while the patients were on study medication for a short period of time (except one never took study medication).

Table 9.2.1.1. Design Features and Numbers of Patients Evaluable for Efficacy by Treatment Group in the U.S. Pivotal, Randomized, Controlled, Double-Blind, Pediatric Studies.

Study features				Placebo	Pulmicort Respules (N=779)						Total
Study #	Pt Age (years)	Inhaled steroid[1]	Duration (Weeks)		0.25 mg		0.5 mg		1.0 mg		
					QD	BID	QD	BID	QD	BID	
04-3069	0.5-8	Naive	12	92	91		82		93		358
04-3072	4-8	Dependent	12	44		47		42		45	178
04-3100	0.5-8	Optional	12	92	93	97		96	93		471
Total	NA	NA	NA	228	184	144	82	138	186	45	1007

[1] Prior to randomization.
Data Source: [133:24, 140-1]

9.2.1.2 Patient Demography and Baseline Characteristics

[133:25-33]

In general, the budesonide and placebo groups were similar with respect to gender, age, race, weight and height within each of three studies. For each study, the majority of the patients were male (61.8% to 66.0%). The mean ages ranged between 52.4 to 59.9 months, 78.3 to 82.2 months, and 53.0 to 57.8 months for Studies 04-3069, 04-3072, and 04-3100, respectively. Overall, 78.4% of the patients were Caucasian, 13.8% African American, and 5.5% Hispanic.

It is noted that numbers of patients younger than one year old in Studies 04-3069 and 04-3100 were significantly less than the targeted enrollments. In all three studies combined, only a total of 13 patients younger than 11 month-old and 26 younger than 1 year-old were evaluated.

Table 9.2.1.2. Numbers of Patients Aged Younger Than One Year in the Pivotal Studies.

Study	Targeted Patient #[1]		Actual patient #		Actual #/Targeted # (%)	
	< 12 M[2]	< 11 M	< 12 M	< 11 M	< 12 M	< 11 M
04-3069	21	18	14	6	67	33
04-3072	0	0	0	0	NA	NA
04-3100	28	24	12	7	43	29
Total	49	41	26	13	53	32

[1] Targeted patient number: the number of patients distributed evenly across the age range stratified by month.
[2] M = month-old.
NA: not applicable.

9.2.1.3 Treatment Discontinuations and Actual Duration of Exposure to Treatment

[133:34-38]

The proportions of patients who discontinued double-blind treatment due to worsening of asthma were consistently higher in the placebo group than in the budesonide groups for all three studies. Numbers of discontinuations for adverse events and other reasons were similar across the treatment groups. Thence, mean durations of actual exposure to double-blind treatment were shorter in the placebo group than budesonide groups combined in all three studies.

Table 9.2.1.3. Numbers of Patients Randomized, Completed or Discontinued and Actual Duration of Treatment in the U.S. Pivotal, Randomized, Controlled, Double-Blind, Pediatric Studies.

Study	Treatment	Randomized[1]	Completed	Discontinued				Actual Duration (Days)[2]
				Adverse Events	Worsening Asthma	Other	Total	
04-3069	Pulmicort 0.25 mg QD	91	74 (81.3%)	2	13	2	17	
	Pulmicort 0.5 mg QD	83	63 (75.9%)	2	14	4	20	77±21
	Pulmicort 1.0 mg QD	93	80 (86.0%)	0	12	1	13	
	Placebo	92	66 (71.7%)	0	21	5	26	73±22
04-3072	Pulmicort 0.25 mg BID	47	41 (87.2%)	0	5	1	6	
	Pulmicort 0.5 mg BID	42	37 (88.1%)	1	1	3	5	79±20
	Pulmicort 1.0 mg BID	45	36 (80.0%)	2	6	1	9	
	Placebo	44	25 (56.8%)	2	16	1	19	64±30
04-3100	Pulmicort 0.25 mg QD	94	74 (78.7%)	0	15	5	20	
	Pulmicort 0.25 mg BID	99	78 (78.8%)	1	13	7	21	75±21
	Pulmicort 0.5 mg BID	98	79 (80.6%)	1	15	3	19	
	Pulmicort 1.0 mg QD	95	66 (69.5%)	2	20	7	29	
	Placebo	95	58 (61.1%)	2	25	10	37	64±31

[1] Randomized and entered into double-blind treatment.
[2] Actual duration of exposure to treatment in days. The data of active treatment groups combined and placebo are shown.
Data Source: [133:35, 38]

9.2.1.4 Efficacy Results of the U.S. Pivotal, Randomized, Controlled, Double-Blind, Pediatric Studies

[133:39-83]

9.2.1.4.1 Primary Efficacy Variables

Because pulmonary function could not be accurately and consistently assessed in children younger than 5 years of age, the improvements in nighttime and daytime asthma symptom scores were considered to be of primary importance in the study of budesonide nebulizing suspension for the treatment of asthma in pediatric patients, as these could be assessed for all children. In all three U.S. pivotal, double-blind studies, changes in mean nighttime and daytime asthma symptom scores from baseline (last seven days prior to randomization) to the double-blind treatment period (Weeks 0-12) were compared between each of the budesonide nebulizing suspension treatment groups and placebo.

9.2.1.4.1.1 Analysis of Nighttime and Daytime Asthma Symptom Scores, All Patients Treated Analysis, Last Value Carried Forward, Total Population

The differences in mean changes in nighttime and daytime asthma symptom scores from baseline to double-blind phase between the budesonide nebulizing suspension groups and placebo are shown in Table 9.2.1.4.1.1. and Figure 9.2.1.4.1.1.

Compared to placebo, each of the budesonide doses resulted in significantly greater improvements in nighttime and daytime symptom scores (with the exception of the 0.25 mg QD dose group in Study 04-3100 for which a numerical improvement compared to placebo was observed). The improvements by budesonide BID regimens were more consistent than those by budesonide QD regimens. After adjusting for multiple comparisons using Dunnett's test, only 4 of 10 budesonide QD dose groups maintained significantly greater improvements in asthma symptom scores compared to the placebo. In contrast, 9 of 10 budesonide BID dose groups remained significantly greater improvements in asthma symptom scores compared to the placebo.

In 3 pivotal studies, there was a total of 20 combinations of dosing regimens and a change in daytime or nighttime asthma symptom score. The maximal improvement was achieved by 4 weeks in 2, by 6 weeks in 8, and by 10 weeks in 16 (Figures 8.1-3.4.4.1.1.C-D).

Table 9.2.1.4.1.1. Mean Changes from Baseline in Primary Efficacy Variables of All Three Pivotal Studies; All Patients Treated, Last Value Carried Forward.[1]

Variable (Weeks 0-12) Mean Change from Baseline[2]		Placebo	Budesonide Nebulizing Suspension					
			0.25 mg QD	0.25 mg BID	0.5 mg QD	0.5 mg BID	1.0 mg QD	1.0 mg BID
thma Symptom Score (scale of 0-3):								
Nighttime								
	Study 04-3069	-0.16	-0.49**	NA	-0.42**	NA	-0.42*	NA
	Study 04-3072	-0.08	NA	-0.36**	NA	-0.37*	NA	-0.36**
	Study 04-3100	-0.13	-0.28	-0.49**	NA	-0.42**	-0.40**	NA
Daytime								
	Study 04-3069	-0.26	-0.57**	NA	-0.46*	NA	-0.50*	NA
	Study 04-3072	-0.11	NA	-0.45**	NA	-0.053**	NA	-0.55**
	Study 04-3100	-0.19	-0.28	-0.40**	NA	-0.46**	-0.37*	NA
Improvements in Primary Variables[4]								
	All Studies	NA	2/4	4/4	1/2	3/4	1/4	2/2

[1] Data sources: Tables 8.1-3.5.
[2] Mean change adjusted for center effect.
[3] For those patients who were able to perform the test.
[4] For each budesonide dose, shown is the number of variables with statistically significant improvements/the total number of variables evaluated in all studies.
* Statistically significantly different from placebo at the .05 level before adjusting for multiple comparisons.
** Statistically significantly different from placebo at the .05 level before and after adjusting for multiple comparisons using Dunnett's test, only performed for asthma symptom score.

9.2.1.4.1.2 Time to Onset of Response, All Patients Treated Analysis, Total Population

The onset of response to budesonide nebulizing suspension in asthma symptom scores was first evaluated using the mean asthma symptom scores over a period of every two weeks. Compared to the placebo group, the onset of numerical improvements in nighttime or daytime asthma symptom scores of each budesonide group was observed by Week 2 (with the exception of nighttime symptom score of 0.50 mg BID budesonide group in Study 04-3072; by Week 4) and was sustained throughout the 12-week treatment phase in all three studies. However, the statistically significant differences for either nighttime or daytime symptom scores in all budesonide groups were not observed until Weeks 4-6 in Studies 04-3069 and 04-3072. In Study 04-3100, the statistically significant differences for daytime symptom scores in all three budesonide groups were observed by Week 4 and for nighttime scores by Week 2. (Sections 8.1-3.4.4.1.1)

If the time to onset responses is defined as the first day associated with a statistically significant difference in changes from the baseline of asthma symptom scores between all budesonide groups combined and placebo, the onsets for nighttime and daytime symptom scores were between Day 2 and Day 4 (except Day 8 for nighttime symptom score in Study 3072) (Table 9.2.1.4.1.2). The numerical superiority of budesonide groups combined over placebo was maintained. However, the statistically significant superiority of budesonide groups combined over placebo in more than half of the first 14 days was only observed in Study 04-3069 for nighttime scores and in Study 04-3072 for daytime scores.

Table 9.2.1.4.1.2. Onset of Response (Improvement of Daytime or Nighttime Asthma Symptom Scores) to Budesonide Nebulizing Supsension Treatment.

Response to Budesonide	Study 04-3069		Study 04-3072		Study 04-3100	
	Nighttime	Daytime	Nighttime	Daytime	Nighttime	Daytime
Onset of Response[1]	Day 4	Day 2	Day 8	Day 3	Day 2	Day 2
Superiority of Budesonide over Placebo[2]						
Numerical (days)[3]	14	14	11	14	14	13
Statistical (days)[4]	11	6	1	10	5	3

[1] Defined as the first day associated with a statistically significant difference in changes from the baseline of asthma symptom scores between budesonide groups combined and placebo.

[2] Defined as the improvements from the baseline of asthma symptom scores of budesonide groups combined are numerically or statistically significantly greater than that of placebo.

[3] The number of days in the first two weeks of treatment phase, in which the improvements from the baseline of asthma symptom scores of budesonide groups combined were numerically greater than that of placebo.

[4] The number of days in the first two weeks of treatment phase, in which the improvements from the baseline of asthma symptom scores of budesonide groups combined were statistically significantly greater than that of the placeb ($p<0.05$).

9.2.1.4.1.3 Dose Response, All Patients Treated Analysis, Last Value Carried Forward, Total Population

In all three pivotal studies, the improvements in nighttime or daytime asthma symptom scores from baseline to the double-blind treatment phase in budesonide groups were not dose-dependent (Table 9.2.1.4.1.1). Before adjusting for multiple comparisons using Dunnett's test, only 0.25 mg QD budesonide regimen did not demonstrate consistently significant improvements in either nighttime or daytime asthma symptom scores. After adjusting for multiple comparisons using Dunnett's test, only BID budesonide regimens yielded consistently significant improvements in both nighttime and daytime asthma symptom scores.

9.2.1.4.1.4 Stratification by Age Group, Gender, or Race; All Patients Treated Analysis, Last Value Carried Forward, Total Population

Changes in nighttime and daytime asthma symptom scores by age group, gender, or race for three U.S. pivotal studies combined are shown in Table 9.2.1.4.1.4A-C, respectively.

By Age group: Patients were categorized into three age groups (6 months to 2 years, greater than 2 years to less than 4 years, and greater than or equal to 4 years). The results demonstrated that budesonide improved nighttime and daytime asthma symptoms in patients in all three age groups compared to placebo although a statistical significance was not always achieved, possibly due to reduced numbers of patients in each group by stratifying. In general, the mean differences in changes in nighttime and daytime asthma symptom scores between budesonide and placebo were comparable between the three age categories.

By Gender: The results demonstrated that budesonide improved nighttime and daytime asthma symptoms in patients for both males and females compared to placebo although a statistical significance was not always achieved, possibly due to reduced numbers of patients in each group by stratifying. In general, the mean differences in changes in nighttime and daytime asthma symptom scores between budesonide and placebo were comparable between males and females.

By Race: Patients were categorized into five race groups (Caucasian, Black, Hispanic, Oriental, Other). The numbers of patients classified as Oriental or Other were too small to draw reasonable conclusions. The results demonstrated that the improvements in nighttime and daytime asthma symptoms by budesonide were less consistent in Black and Hispanic patients compared to Caucasian patients. In this regard, 5/12 Black groups and 3/12 of Hispanic groups failed to demonstrate numerical improvements in asthma symptom scores compared to placebo.

Table 9.2.1.4.1.4A. Nighttime and Daytime Asthma Symptom Scores: Differences Between Budesonide Nebulizing Suspension and Placebo in Mean Changes* From Baseline to Double-Blind Treatment (Weeks 0-12) in Three Pivotal Studies Combined; All Patients Treated Analysis, Last Value Carried Forward, Total Population By Age Group.

Combined Studies	Age Group	Summary Statistic	BUDESONIDE TREATMENT GROUP					
			0.25 mg QD	0.25 mg BID	0.5 mg QD	0.5 mg BID	1.0 mg QD	1.0 mg BID
Nighttime	6 Months-2 Years	N	13	10	10	10	17	NA
		Difference From Placebo	-0.95	-0.71	-0.50	-0.93	-0.36	
		(95% CI)	(-1.54, -0.36)	(-1.35, -0.08)	(-1.13, 0.14)	(-1.56, -0.29)	(-0.91, 0.20)	
		p-value	0.011	0.082	0.270	0.039	0.283	
	>2-<4 Years	N	65	32	27	39	56	NA
		Difference From Placebo	-0.30	-0.47	-0.40	-0.38	-0.53	
		(95% CI)	(-0.56, -0.05)	(-0.78, -0.16)	(-0.73, -0.08)	(-0.67, -0.09)	(-0.79, -0.27)	
		p-value	0.031	0.009	0.029	0.022	<0.001	
	≥ 4 Years	N	106	102	45	89	113	44
		Difference From Placebo	-0.25	-0.35	-0.27	-0.26	-0.18	-0.24
		(95% CI)	(-0.40, -0.10)	(-0.50, -0.19)	(-0.47, -0.07)	(-0.42, -0.10)	(-0.33, -0.04)	(-0.44, -0.04)
		p-value	0.001	<0.001	0.014	0.002	0.018	0.028
Daytime	6 Months-2 Years	N	13	10	10	10	17	NA
		Difference From Placebo	-0.82	-0.37	-0.29	-1.05	-0.19	
		(95% CI)	(-1.45, -0.19)	(-1.05, 0.31)	(-0.97, 0.39)	(-1.72, -0.37)	(-0.78, 0.41)	
		p-value	0.036	0.385	0.538	0.029	0.595	
	>2-<4 Years	N	64	32	27	39	56	NA
		Difference From Placebo	-0.16	-0.19	-0.27	-0.39	-0.38	
		(95% CI)	(-0.42, 0.09)	(-0.49, 0.12)	(-0.59, 0.06)	(-0.68, -0.10)	(-0.64, -0.11)	
		p-value	0.244	0.298	0.148	0.021	0.009	
	≥ 4 Years	N	106	102	45	89	113	45
		Difference From Placebo	-0.25	-0.32	-0.24	-0.31	-0.18	-0.34
		(95% CI)	(-0.40, -0.10)	(-0.47, -0.17)	(-0.44, -0.04)	(-0.46, -0.15)	(-0.33, -0.04)	(-0.54, -0.14)
		p-value	0.001	<0.001	0.026	<0.001	0.019	0.002

* Mean Change Adjusted for Center Effect.
NA: Not Applicable.
Data Source: [133:153-4].

Table 9.2.1.4.1.4B. Nighttime Asthma Symptom Scores: Differences Between Budesonide Nebulizing Suspension and Placebo in Mean Changes* From Baseline to Double-Blind Treatment (Weeks 0-12) in Three Pivotal Studies Combined; All Patients Treated Analysis, Last Value Carried Forward, Total Population By Gender.

Combined Studies	Gender	Summary Statistic	BUDESONIDE TREATMENT GROUP					
			0.25 mg QD	0.25 mg BID	0.5 mg QD	0.5 mg BID	1.0 mg QD	1.0 mg BID
Nighttime	Male	N	121	92	58	97	117	29
		Difference From Placebo	-0.26	-0.29	-0.29	-0.25	-0.21	-0.28
		(95% CI)	(-0.43, -0.10)	(-0.47, -0.11)	(-0.49, -0.08)	(-0.43, -0.08)	(-0.37, -0.04)	(-0.55, -0.01)
		p-value	0.002	0.003	0.011	0.008	0.017	0.051
	Female	N	63	52	24	41	69	15
		Difference From Placebo	-0.08	-0.30	-0.15	-0.21	-0.30	-0.08
		(95% CI)	(-0.27, 0.12)	(-0.50, -0.10)	(-0.42, 0.12)	(-0.43, 0.01)	(-0.49, -0.12)	(-0.41, 0.25)
		p-value	0.468	0.010	0.309	0.095	0.004	0.648
Daytime	Male	N	120	92	58	97	117	29
		Difference From Placebo	-0.23	-0.18	-0.19	-0.29	-0.22	-0.29
		(95% CI)	(-0.39, -0.06)	(-0.36, -0.01)	(-0.39, 0.02)	(-0.46, -0.11)	(-0.38, -0.05)	(-0.56, -0.02)
		p-value	0.008	0.057	0.102	0.003	0.012	0.044
	Female	N	63	52	24	41	69	16
		Difference From Placebo	-0.09	-0.24	-0.18	-0.25	-0.23	-0.37
		(95% CI)	(-0.27, 0.09)	(-0.43, -0.05)	(-0.42, 0.07)	(-0.46, -0.04)	(-0.40, -0.05)	(-0.67, -0.07)
		p-value	0.364	0.028	0.200	0.037	0.022	0.024

* Mean Change Adjusted for Center Effect.
NA: Not Applicable.
Data Source: [133:158-9].

Table 9.2.1.4.1.4C. Nighttime Asthma Symptom Scores: Differences Between Budesonide Nebulizing Suspension and Placebo in Mean Changes* From Baseline to Double-Blind Treatment (Weeks 0-12) in Three Pivotal Studies Combined; All Patients Treated Analysis, Last Value Carried Forward, Total Population By Race.

Combined Studies	Race	Summary Statistic	BUDESONIDE TREATMENT GROUP					
			0.25 mg QD	0.25 mg BID	0.5 mg QD	0.5 mg BID	1.0 mg QD	1.0 mg BID
Nighttime	Caucasian	N	138	113	57	115	143	39
		Difference From Placebo	-0.24	-0.33	-0.31	-0.28	-0.28	-0.33
		(95% CI)	(-0.38, -0.11)	(-0.48, -0.19)	(-0.49, -0.12)	(-0.43, -0.14)	(-0.42, -0.15)	(-0.55, -0.12)
		p-value	0.001	<0.001	0.002	<0.001	<0.001	0.005
	Black	N	32	24	15	14	23	2
		Difference From Placebo	-0.05	-0.25	0.35	-0.08	0.18	0.49
		(95% CI)	(-0.42, 0.31)	(-0.63, 0.14)	(-0.10, 0.79)	(-0.53, 0.38)	(-0.21, 0.58)	(-0.53, 1.51)
		p-value	0.797	0.301	0.227	0.783	0.441	0.381
	Hispanic	N	10	5	7	5	12	3
		Difference From Placebo	-0.38	-0.05	-0.61	-0.62	-0.79	0.85
		(95% CI)	(-0.97, 0.20)	(-0.80, 0.70)	(-1.27, 0.05)	(-1.37, 0.13)	(-1.34, -0.23)	(-0.07, 1.78)
		p-value	0.310	0.927	0.160	0.301	0.029	0.186
Daytime	Caucasian	N	138	113	57	115	143	40
		Difference From Placebo	-0.23	-0.24	-0.27	-0.34	-0.25	-0.42
		(95% CI)	(-0.36, -0.09)	(-0.38, -0.10)	(-0.45, -0.09)	(-0.48, -0.20)	(-0.39, -0.12)	(-0.63, -0.21)
		p-value	0.001	0.002	0.007	<0.001	<0.001	<0.001
	Black	N	31	24	15	14	23	2
		Difference From Placebo	-0.05	-0.22	0.56	-0.09	0.22	-0.14
		(95% CI)	(-0.43, 0.33)	(-0.63, 0.18)	(0.09, 1.02)	(-0.57, 0.38)	(-0.19, 0.62)	(-1.20, 0.92)
		p-value	0.824	0.360	0.062	0.748	0.384	0.804
	Hispanic	N	10	5	7	5	12	3
		Difference From Placebo	-0.43	0.02	-0.82	-0.30	-0.67	0.77
		(95% CI)	(-1.02, 0.17)	(-0.75, 0.79)	(-1.50, -0.15)	(-1.06, 0.47)	(-1.23, -0.10)	(-0.18, 1.71)
		p-value	0.269	0.969	0.068	0.623	0.066	0.241

* Mean Change Adjusted for Center Effect.
NA: Not Applicable.
Data Source: [133:164-5].

9.2.1.4.2 *Secondary Efficacy Variables*

The mean changes of secondary efficacy variables from baseline to double-blind phase of three pivotal studies are summarized in Table 9.2.1.4.2.

Compared to placebo, all budesonide dose groups demonstrated numerical improvements in secondary efficacy variables except morning PEF of 0.5 mg QD budesonide group and $FEF_{25-75\%}$ of 0.25 mg QD budesonide group in Study 04-3069. In all three studies, the improvements in secondary efficacy variables from baseline to the double-blind treatment phase in budesonide groups were not dose-dependent. Consistent with the observation of primary efficacy variables (Table 9.2.1.4.1.1), the improvements of secondary efficacy variables by budesonide BID regimens were more consistent compared to budesonide QD regimens. In total, only 11 of 35 budesonide QD dose groups demonstrated significantly greater improvements compared to placebo. In contrast, 22 of 35 budesonide BID dose groups showed significantly greater improvements compared to the placebo.

Table 9.2.1.4.2. Mean changes from baseline in secondary efficacy variables; All Patients Treated, Last Value Carried Forward.[1]

Variable (Weeks 0-12) Mean Change from Baseline[2]		Placebo	Budesonide Nebulizing Suspension					
			0.25 mg QD	0.25 mg BID	0.5 mg QD	0.5 mg BID	1.0 mg QD	1.0 mg BID
Use of Breakthrough Medication (days)								
	Study 04-3069	-4.19	-6.26*	NA	-6.31*	NA	-5.98*	NA
	Study 04-3072	-3.14	NA	-5.56*	NA	-6.66*	NA	-6.00
	Study 04-3100	-2.36	-4.39*	-5.22*	NA	-4.92*	-4.38*	NA
PEF[3]:								
Morning								
	Study 04-3069	7.1	14.4	NA	6.5	NA	10.9	NA
	Study 04-3072	-1.3	NA	15.3*	NA	11.8*	NA	10.4*
	Study 04-3100	-0.2	10.9	23.0*	NA	24.8*	17.1*	NA
Evening								
	Study 04-3069	3.6	11.2	NA	3.8	NA	9.9	NA
	Study 04-3072	3.0	NA	14.9*	NA	11.6	NA	13.2
	Study 04-3100	1.9	16.8	19.2*	NA	21.0*	14.1	NA
Spirometry[3]:								
FEV_1 (L)								
	Study 04-3069	-0.07	-0.01	NA	0.03*	NA	0.03*	NA
	Study 04-3072	-0.01	NA	0.05	NA	0.08*	NA	0.07
	Study 04-3100	0.04	0.07	0.08	NA	0.17*	0.11	NA
FVC (L)								
	Study 04-3069	-0.04	0.05	NA	0.06*	NA	0.04	NA
	Study 04-3072	0.04	NA	0.09	NA	0.06	NA	0.05
	Study 04-3100	0.00	16.8	19.2	NA	21.0*	14.1	NA
$FEF_{25-75\%}$ (L/sec)								
	Study 04-3069	-0.09	-0.10	NA	0.01	NA	-0.05	NA
	Study 04-3072	-0.06	NA	0.00	NA	0.14*	NA	0.14*
	Study 04-3100	0.07	0.10	0.08	NA	0.23	0.20	NA
Patients Discontinued (%)[4]								
	Study 04-3069	28	19	NA	24	NA	14*	NA
	Study 04-3072	43	NA	13*	NA	12*	NA	20*
	Study 04-3100	39	21*	21*	NA	19*	31	NA
Improvements in Secondary Variables[5]								
	All Studies	NA	3/14	8/14	3/7	11/14	5/14	3/7

[1] Data sources: Tables 8.1-3.5.
[2] Mean change adjusted for center effect.
For those patients who were able to perform the test.
Using Fisher's exact test for comparison.
[5] For each budesonide dose, shown is the number of variables with statistically significant improvements/the total number of variables evaluated in all studies.
* Statistically significantly different from placebo at the .05 level without adjusting for multiple comparisons.

9.2.2 *A Controlled, Open-label, 52-Week Trial Extension to Study 04-3069 (Study 04-3069B)*

See Sections 8.4.4.4.1-7 and Table 8.4.5.

9.3 Non-U.S. Supportive Clinical Studies

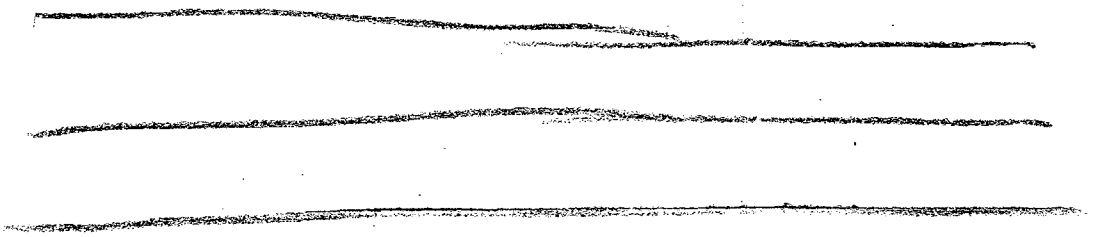
[133:103-122]

The synopses of 13 non-U.S. studies classified as completed supportive studies in evaluating the efficacy of budesonide nebulizing suspension for the treatment of persistent asthma were included in ISE of the sponsor's NDA. Eleven of these studies were controlled studies and 2 studies were uncontrolled. These 2 uncontrolled studies were related to the oral steroid-sparing capacity of budesonide nebulizing suspension. Four of the 13 studies included an evaluation of the oral steroid-sparing capacity of budesonide nebulizing suspension (Study 04-2213 in asthmatic children aged 5 years or less, and other 3 studies in asthmatic adults). Study 04-2213 is the only supportive study reviewed in this section.

9.3.1 *An Oral Steroid-Sparing Pediatric Study (04-2213): Budesonide Suspension for Nebulization in Infants with Asthma*

See Sections 8.5.1.1-4 for details.

Thirty-seven asthmatic patients aged between 9 and 60 months (mean = 26.7±13 months) were randomized into a double-blind, placebo-controlled, parallel-group study to evaluate the steroid-sparing effect of budesonide nebulizing suspension. After a run-in period of two to four weeks, the eligible children were randomized to either 1.0 mg BID budesonide nebulizing suspension or nebulized placebo for eight weeks. During each week of the double-blind treatment period, parents were instructed to reduce their child's oral prednisolone dose by 25-33% of the initial dose provided that the child was symptom-free during the previous week, or had fewer symptoms than in the previous week and did not require an inhaled bronchodilator (terbutaline) more than once a day during the preceding week.



9.4 Conclusions and Comments

Results from the three U.S. pivotal, randomized, controlled, double-blind studies (12 weeks) and the one controlled open-label study (1 year) in pediatric asthma patients aged 6 months to 8 years demonstrated the following:

- Administration of budesonide nebulizing suspension in doses of 0.25, 0.5, and 1.0 mg, QD or BID resulted in improvements in nighttime and daytime asthma symptom scores compared to placebo. The improvements by BID regimens were more consistent than those by QD

regimens. After adjusting for multiple comparisons, 4 of 10 QD groups and 9 of 10 BID groups maintained statistically significantly greater improvements compared to the placebo.

- The onset of improvement in asthma symptoms can occur within 2 to 4 days of beginning treatment, although maximum benefit may not be achieved for 4 to 6 weeks, or longer.
- Administration of budesonide nebulizing suspension in doses of 0.25, 0.5, and 1.0 mg, QD or BID resulted in improvements in most of secondary variables compared to placebo, which included the following: days of bronchodilator therapy, the proportion of patients who were discontinued from the study for any reason as well as morning and evening PEFs, FEV_1, FVC, and $FEF_{25-75\%}$ in the subgroup of patients capable of performing the testing. Same as for primary efficacy variables, the improvements of secondary efficacy variables by BID regimens were more consistent compared to QD regimens. Of these variables, 11of 35 QD groups and 22 of 35 BID groups demonstrated statistically significantly greater improvements compared to placebo.
- For the efficacy profile of budesonide nebulizing suspension, no apparent effect of age or gender was observed. The improvements in nighttime and daytime asthma symptoms by budesonide appeared less consistent in Black and Hispanic patients compared to Caucasian patients. In this regard, 5 of 12 Black groups and 3 of 12 of Hispanic groups failed to demonstrate numerical improvements in asthma symptom scores compared to placebo.
- Dose-related improvements in primary or secondary variables were not demonstrated for budesonide nebulizing suspension.
- The improvements in efficacy variables were less consistent in the 52-week open-label study compared to the 12-week double-blind studies.

Of note, the number of patients younger than 1 year of age was very small. In three pivotal studies, only a total of 13 patients younger than 11 months of age and 26 younger than 1 year of age were evaluated.

In addition, 1.0 mg BID budesonide nebulization suspension was not studied in patients younger than 4 years of age in three pivotal studies although it was evaluated in some smaller scale supportive studies. In children aged between 4 and 8 years, 1.0 mg BID budesonide was not more effective than 0.5 mg BID regimen in a pivotal study (04-3072).

It should be also noted that a Pari LC-Jet Plus Nebulizer (with face mask or mouthpiece) and a Pari Master compressor were used to delivered budesonide nebulizing suspension in all three pivotal studies. No other nebulizing devices have been used in the pivotal studies and the efficacy of budesonide nebulizing suspension delivered by other devices is uncertain.

10. INTEGRATED SUMMARY OF SAFETY (ISS)

10.1 Introduction

The purpose of this summary is to integrate into one document the safety results of studies of budesonide nebulizing suspension (Pulmicort Respules) for the maintenance treatment of asthma as prophylactic therapy in children between the ages of six months and eight years. The focus of this summary is on the safety profile of Pulmicort Respules demonstrated in three pivotal, randomized, double-blind, placebo-controlled, parallel-group studies conducted in the U.S.. The completed non-U.S. supportive clinical studies and post-marketing experience will be reviewed also.

10.2 U.S. Pivotal Clinical Studies

10.2.1 Three Randomized, Controlled, Double-Blind, Pediatric Studies (04-3069, 04-3072, 04-3100)

10.2.1.1 Design Features and Numbers of Patients

Of the 1,018 patients who were randomized into three U.S. pivotal pediatric studies, 1,017 patients were evaluable for safety (one patient from Study 04-3100, who discontinued on the first day and never took study medication, was not included).

Table 10.2.1.1. Design Features and Numbers of Patients Evaluable for Safety by Treatment Group in the U.S. Pivotal, Randomized, Controlled, Double-Blind, Pediatric Studies.

Study features				Placebo	Pulmicort Respules (N=786)						Total
Study #	Pt Age (years)	Inhaled steroid[1]	Duration (Weeks)		0.25 mg		0.5 mg		1.0 mg		
					QD	BID	QD	BID	QD	BID	
04-3069	0.5-8	Naive	12	92	91		83		93		359
04-3072	4-8	Dependent	12	44		47		42		45	178
04-3100	0.5-8	Optional	12	95	94	99		97	95		480
Total	NA	NA	NA	231	185	146	83	139	188	45	1017

[1] Prior to randomization.

10.2.1.2 Patient Demography and Baseline Characteristics

See Section 9.2.1.2 for details. In all three studies combined, only a total of 13 patients younger than 11 months of age and 26 younger than 1 year of age were evaluated.

10.2.1.3 Treatment Discontinuations and Actual Duration of Exposure to Treatment

The proportions of patients who discontinued double-blind treatment due to worsening of asthma were consistently higher in the placebo group compared to each Pulmicort Respules group in all three studies (see Table 9.2.1.3). Thence, in each study the mean duration of actual exposure to treatment was shorter in the placebo group compared to each Pulmicort

Respules group. When the data of three studies were pooled, the mean duration of treatment remained slightly longer in each Pulmicort Respules dose group compared to placebo and was similar among different Pulmicort Respules dose groups.

Table10.2.1.3: Duration of Exposure. Data are Pooled from the Three U.S. Pivotal Pulmicort Respules Studies (N=1,017). [134:39]

Duration of Treatment (Days)	Placebo (n=231)	Total Pulmicort Respules (n=786)	Pulmicort Respules Total Daily Dose			
			0.25 mg (n=185)	0.5 mg (n=229)	1.0 mg (n=327)	2.0 mg (n=45)
Mean ± SD	67±29	76±22	76±22	75±24	76±21	77±20
Median	83	84	84	84	84	84
25% Percentile	53	81	82	82	81	81
75% Percentile	85	85	85	86	85	86

Data Source: [135:45]

10.2.1.4 Reported Adverse Events

The proportions of patients experiencing adverse events, serious adverse events, or discontinuing due to an adverse event were comparable between the placebo and Pulmicort Respules groups.

Table 10.2.1.4A: Summary of Reported Adverse Events. Data are Pooled from the Three U.S. Pivotal Pulmicort Respules Studies (N=1,017). [134:44]

	Placebo (n=231)	Total Pulmicort Respules (n=786)	Pulmicort Respules Total Daily Dose			
			0.25 mg (n=185)	0.5 mg (n=229)	1.0 mg (n=327)	2.0 mg (n=45)
No. Patients with an AE	190 (82%)	635 (81%)	146 (79%)	187 (82%)	267 (82%)	35 (78%)
No. Patients with a Serious AE	6 (3%)	17 (2%)	6 (3%)	4 (2%)	7 (2%)	0 (0%)
No. Patients Who Discontinued from the studies due to an AE	4 (2%)	11 (1%)	2 (1%)	3 (1%)	4 (1%)	2 (4%)

In the Pulmicort Respules group, the most frequently reported adverse events were respiratory infection (36%), fever (18%), sinusitis (13%), otitis media (10%), and rhinitis (10%). The reported incidences of these adverse events in the total Pulmicort Respules group were less than or equal to those of the placebo group.

Among adverse events with an incidence of ≥3% in the total Pulmicort Respules group, the incidences of coughing (7%), ear infection NOS (Not Otherwise Specified) (5%), viral infection (4%), moniliasis (4%), abdominal pain (3%), and epistaxis (3%) were higher in Pulmicort Respules group.

Table 10.2.1.4B: Adverse Events with an Incidence of ≥3% in the Total Pulmicort Respules Group by Body System and Preferred Term. Data are Pooled from the Three U.S. Pivotal Pulmicort Respules Studies (N=1,017). [134:45]

	Placebo (n=231)	Total Pulmicort Respules (n=786)
Respiratory System Disorders		
Respiratory Infection	84 (36%)	286 (36%)
Sinusitis	40 (17%)	104 (13%)
Rhinitis	22 (10%)	82 (10%)
Coughing	12 (5%)	56 (7%)
Pharyngitis	16 (7%)	44 (6%)
Bronchospasm	15 (6%)	28 (4%)
Bronchitis	13 (6%)	28 (4%)
Body as a Whole-General Disorders		
Fever	53 (23%)	142 (18%)
Accident and/or Injury	19 (8%)	60 (8%)
Pain	6 (3%)	23 (3%)
Resistance Mechanism Disorders		
Otitis Media	28 (12%)	81 (10%)
Infection Viral	6 (3%)	31 (4%)
Moniliasis	5 (2%)	31 (4%)
Gastro-Intestinal System Disorders		
Gastroenteritis	11 (5%)	43 (5%)
Vomiting	8 (3%)	27 (3%)
Diarrhoea	6 (3%)	23 (3%)
Abdominal Pain	5 (2%)	20 (3%)
Central and Peripheral Nerve System Disorders		
Headache	19 (8%)	56 (7%)
Hearing and Vestibular Disorders		
Ear Infection NOS[1]	10 (4%)	37 (5%)
Platelet, Bleeding, and Clotting Disorders		
Epistaxis	3 (1%)	24 (3%)

[1] NOS: Not Otherwise Specified.

Among adverse events with an incidence of 1-<3% in the total Pulmicort Respules group, the incidences of flu-like disorder (2%), earache (2%), eczema (1%), hyperkinesia, and contact dermatitis (1%) were higher in Pulmicort Respules group. [134:56-63]

10.2.1.4.1 Adverse Events by Daily Dose

[134:46-7]

Among adverse events with an incidence of ≥3% in the total Pulmicort Respules group, a dose-related increase in incidence was not apparent for most adverse events. Incidences of stridor (4%), flu-like disorder (4%), external ear infection (4%), and application site reaction (4%) were more than twofold in the 2.0 mg Pulmicort Respules daily dose group compared to other treatment groups including placebo. These adverse events might be dose dependent.

10.2.1.4.2 Adverse Events by Gender

[134:48-9]

Among adverse events with an incidence of ≥3% in the total Pulmicort Respules group, incidences of most adverse events were similar for male and female patients. The incidences of pharyngitis and headache were higher (2 and 1.7 folds, respectively) in female patients and the incidence of accident and/or injury was higher (1.5 folds) in male patients.

10.2.1.4.3 Adverse Events by Age

[134:50-1]

There was no apparent effect of age on the incidences of most adverse events. Among Pulmicort Respules groups, the following adverse events were more frequent in patients aged 6 months to 2 years compared to patients aged between 2 and 4 years as well as 4 and 8 years: respiratory infection, rhinitis, bronchitis, otitis media, moniliasis, gastroenteritis, mouth disorder, skin rash, ear infection NOS, anorexia, and increased alkaline phosphatase. Among these, the incidences of respiratory infection, bronchitis, ear infection NOS, anorexia, and increased alkaline phosphatase were higher in Pulmicort Respules group (48, 10, 20, 3, and 3%, respectively) compared to the placebo group (36, 0, 9, 0, and 0%, respectively).

10.2.1.4.4 Adverse Events by Race

[134:52-5]

The sample sizes for Asian and Other ethnic groups were too small to provide valid comparisons of adverse event incidences between treatment groups. In general, within each racial group (Caucasian, Black, and Hispanic) the adverse event incidences appeared comparable between the Pulmicort Respules and placebo groups.

10.2.1.4.5 Adverse Events by Intensity of Adverse Events

[134:56-8]

Among adverse events with an incidence of ≥3% in the Pulmicort Respules group classified by intensity (mild, moderate, and severe), the incidences were comparable between the Pulmicort Respules group and placebo within each category.

10.2.1.4.6 Adverse Events by Time to Onset

[134:58-9]

Among adverse events with an incidence of ≥3% in the Pulmicort Respules group classified by time to onset (≤1 week, 1⁺-4 weeks, 4⁺-8 weeks, and >8 weeks), the incidences were comparable between the Pulmicort Respules group and placebo within each category.

10.2.1.5 Serious Adverse Events

[134:60-73]

No deaths were reported in the three U.S. pivotal studies. Twenty-three patients experiencing 27 serious adverse events during the double-blind treatment phase were reported (See Sections 8.1-2.4.5.2.4 and 8.3.4.4.2.4 for details). The incidences of serious adverse events were similar between the Pulmicort Respules (2%) and placebo (3%) groups. The respective incidences were 3%, 2%, and 2% for 0.25 mg, 0.5 mg and 1.0 mg Pulmicort Respules total daily dose groups. No serious adverse event was observed for the highest Pulmicort Respules dose group (i.e., 1.0 mg BID). The most common event was bronchospasm. All patients were completely recovered from the serious adverse events. Only one serious adverse event (laryngismus) was determined by the investigator to be associated with the use of study medication.

10.2.1.6 Discontinuations Due to Adverse Events

[134:73-9]

A total of 15 patients (experiencing 19 adverse events during the treatment phase) were discontinued from the three U.S. pivotal studies due to adverse events; 4 (2%) patients were in the placebo group; and 11 patients (1%) were in the Pulmicort Respules group including 2 (1%) in the total daily dose of 0.25 mg, 3 (1%) in the 0.5 mg group, 4 (1%) in the 1.0 mg group, and 2 (4%) in the 2.0 mg group (See Sections 8.1-2.4.5.2.4 and 8.3.4.4.2.4 for details). The most frequent adverse event resulting in study discontinuation in patients receiving Pulmicort Respules was bronchospasm (5 patients). All patients were completely recovered from the adverse events. Three discontinuations were judged to be possibly or probably caused by the study medication.

10.2.1.7 Clinical Laboratory Evaluations

[134:81-3]

The incidence of laboratory adverse events was small and comparable between placebo and Pulmicort Respules groups, accounting for 5 (2.2%) and 10 (1.3%), respectively. The most frequently observed laboratory abnormalities were abnormal blood cell counts followed by alkaline phosphatase elevation. All of the laboratory adverse events were nonserious, mild or moderate in intensity. All but one (lymphocytosis) were judged to be unlikely caused by the study drugs.

10.2.1.8 Physical Examinations

[134:83-6]

The number of people experiencing adverse events determined by physical examination was small and the incidence was comparable between placebo and Pulmicort Respules groups, accounting for 7 (3.0%) and 26 (3.3%), respectively. The most frequently observed abnormalities from physical examinations were ear illnesses (e.g., otitis media, ear infection) followed by respiratory infections. All of the physical examination adverse events were considered non-serious, and mild or moderate in intensity. In the Pulmicort Respules groups, five events (15.6%; 4 moniliasis and 1 with white patchy lesion on right

buccal mucosa) were judged by the investigators to be possibly or probably caused by the study drugs compared to one (11.1%; moniliasis) in the placebo group.

10.2.1.9 Oropharyngeal Fungal Cultures

[134:212-3]

The incidence of positive oral fungal culture increased from Week 0 (36%) to Week 52 (42%) in the Pulmicort Respules group. In contrast, the incidence decreased from Week 0 (38%) to Week 52 (32%) in the placebo group. This finding is not unexpected and consistent with clinical observation that the incidence of oral moniliasis is increased in patients using oral steroid inhalers.

Table 10.2.1.9. Oral Fungal Culture Results. Data are Pooled from the Three U.S. Pivotal Pulmicort Respules Clinical Studies. [134:213]

	Week 0		Week 12	
	Placebo (n=231)	Total Pulmicort Respules (n=786)	Placebo (n=231)	Total Pulmicort Respules (n=786)
No Growth	134 (58%)	471 (60%)	124 (54%)	404 (51%)
Growth	87 (38%)	286 (36%)	73 (32%)	332 (42%)
Minimum Growth	24 (10%)	83 (11%)	26 (11%)	89 (11%)
Moderate Growth	32 (14%)	63 (8%)	20 (9%)	87 (11%)
Heavy Growth	31 (13%)	140 (18%)	27 (12%)	156 (20%)
Missing	10 (4%)	29 (4%)	34 (15%)	50 (6%)

Three patients experienced clinically relevant fungal infections considered to be adverse events. They were all in the Pulmicort Respules groups, including two in 1.0 mg, and one in 2.0 mg total daily doses.

10.2.1.10 HPA-Axis Suppression

[134:195-207]

In Studies 04-3072 and 04-3100, the adjusted mean changes in ACTH-stimulated cortisol levels from baseline were more negative in highest dose groups (-56.3 and -44.1 nmol/L in 1.0 mg BID and 1.0 mg QD groups, respectively) compared to the placebo (-9.1 and -28.1 nmol/L, respectively) (Tables 8.1.4.5.3A and 8.3.4.4.3A).

When the data were pooled from three pivotal studies and stratified by total Pulmicort Respules daily dose, the adjusted mean changes in ACTH-stimulated cortisol levels from baseline were more negative in 2.0 mg group (-35.1 nmol/L) compared to placebo (-27.9 nmol/L) although the difference was not statistically different.

Table 10.2.1.10A. Changes in Basal and ACTH-stimulated Plasma Cortisol Levels by Total Pulmicort Respules Daily Dose. Data are Pooled from the Three U.S. Pivotal Studies. [134:199]

	Basal (nmol/L)			ACTH-Stimulated (nmol/L)					
Total daily dose	**n**	**Baseline**	**Week 12**	**n**	**Baseline**	**Week 12**	**Adjusted Change***	**95% CI on Adj. Change**	**p-Value vs. placebo**
Placebo	64	300	290	61	669	635	-27.9	-69, 14	-
0.25 mg	56	288	296	58	652	662	22.5	-21, 66	0.073
0.5 mg	69	312	293	66	675	671	-2.8	-44, 38	0.355
1.0 mg	91	301	298	92	658	647	-2.3	-37, 32	0.313
2.0 mg	13	241	257	13	602	555	**-35.1**	-136, 66	0.885

* Mean change from baseline in ACTH-stimulated cortisol levels adjusted for center effect.

Stratified by gender, the adjusted mean changes in ACTH-stimulated cortisol levels from baseline remained more negative in 2.0 mg total daily dose groups of males and females (-47.4 and -37.9 nmol/L, respectively) compared to placebo (-39.6 and -15.9 nmol/L).

Stratified by age, the adjusted mean changes in ACTH-stimulated cortisol levels from baseline in 6 months - 2 years group were more negative in all total daily dose groups compared to placebo. In patients aged 4^{+} - 8 years, a similar finding was observed in 2.0 mg group.

- These data suggest a measurable systemic effect of Pulmicort Respules.

Table 10.2.1.10B. Changes in Basal and ACTH-stimulated Plasma Cortisol Levels by Age. Data are Pooled from the Three U.S. Pivotal Studies. [134:203]

	Basal (nmol/L)			ACTH-Stimulated (nmol/L)				
Total daily dose	**n**	**Baseline**	**Week 12**	**n**	**Baseline**	**Week 12**	**Adjusted Change***	**95% CI on Adj. Change**
6 Months - 2 Years								
Placebo	3	296	361	3	701	793	89.8	-595, 775
0.25 mg	5	253	221	5	735	655	**-35.9**	-295, 223
0.5 mg	5	363	379	5	846	695	**-144**	-416, 128
1.0 mg	8	265	248	8	716	703	**-19.4**	-197, 158
2⁺ - 4 Years								
Placebo	16	267	290	14	733	602	-167	-264, -70
0.25 mg	16	316	298	18	657	707	81.9	-2, 165
0.5 mg	15	426	282	14	666	668	-17.2	-117, 83
1.0 mg	26	308	318	28	710	659	-57.3	-126, 11
4⁺ - 8 Years								
Placebo	45	312	286	44	646	635	-1.5	-51, 48
0.25 mg	35	280	306	35	637	640	6.5	-50, 63
0.5 mg	49	272	288	47	659	669	11.2	-37, 59
1.0 mg	57	303	296	56	623	633	16.6	-27, 60
2.0 mg	13	241	257	13	602	555	**-29.7**	-129, 69

* Mean change from baseline in ACTH-stimulated cortisol levels adjusted for center effect.

10.2.2 A Controlled, Open-label, 52-Week Trial Extension to Study 04-3069 (Study 04-3069B)

[134:145-165]

See Sections 8.4.4.5.1-7.

Of note, there was a decrease in the adjusted mean change in ACTH-stimulated cortisol levels from baseline in the Pulmicort Respules group (-22.3 nmol/L) compared to the conventional asthma therapy group (39.1 nmol/L) (See Section 8.4.4.5.3 for details). In the budesonide group, 14% of patients who had normal responsiveness in ACTH-stimulated cortisol levels at baseline showed abnormal responsiveness at Week 52 as compared to 0% in the conventional asthma therapy group. Stratified by gender, the adjusted mean changes in ACTH-stimulated cortisol levels from baseline remained more negative in males (-9.1 nmol/L) and females (-70.6 nmol/L) of the Pulmicort Respules group. The data suggest a measurable systemic effect of long-term use of Pulmicort Respules. In addition, either as a whole group or stratified by gender, the mean measured growth velocity (cm/year) of patients on budesonide was numerically smaller than that of patients on conventional asthma therapy (0.84, 0.9, and 0.65 cm/year for all patients, male patients, and female patients, respectively) (see Section 8.4.4.5.7 for details).

10.3 Completed Non-U.S. Supportive Studies

[134:87-119]

The safety data from patients with asthma enrolled in 20 non-U.S. supportive studies of Pulmicort Respules were provided by the sponsor in the ISS of NDA. Data from more than 514 patients from 14 completed studies of Pulmicort Respules are reviewed in this section. These studies included 3 placebo-controlled studies, 7 dose-comparison controlled studies, 1 active-controlled study, and 3 uncontrolled studies. In these studies, patients used various nebulizer/compressor systems and various total daily doses (0.5-8 mg) of Pulmicort Respules.

10.3.1 Serious Adverse Events

[134:88-117]

10.3.1.1 Death

One newborn death was reported from Study 04-2151 which investigated dose equivalency of Pulmicort Respules and Pulmicort pMDI. Following 23 days of treatment with budesonide pMDI 800mcg BID, a 41 year old female patient with asthma discontinued from the study due to pregnancy. Seven months later, a female child with multiple malformations was born by cesarean section. The child was cyanotic and was placed on a ventilator shortly after birth. Eight days after birth, the child died of bradycardia. The investiagator was unable to classify the causal relationship between the study drug and the multiple malformations and bradycardia.

10.3.1.2 Serious Adverse Events Other than Death

A total of 74 serious adverse events other than deaths were reported. The most frequently reported serious adverse event was asthma aggravated (46 events), followed by respiratory infection/pneumonia (12 events), gastroenteritis (3 events), and backpain (2 events). Each of the remaining adverse events occurred only once.

10.3.2 Discontinuation due to Adverse Events

Seven (~1%) discontinuations due to adverse events were reported. There casual relationships between the treatment and the events of epistaxis, moniliasis, and coughing were possible.

Table 10.3.2: List of Patients Discontinued due to Adverse Events: Pulmicort Respules Completed Supportive Studies. [134:117]

Study Code	Patient No.	Treatment	Adverse Event in Astra AED Preferred Term	Maximum Intensity	Outcome
04-3035	802	Pulmicort Respules 0.25mg BID	Atelectasis	Severe	Complete recovery
04-9239	22	Pulmicort Respules	Asthma Aggravated	Severe	Complete recovery
04-9239	51	Pulmicort Respules	Epistaxis	Moderate	Complete recovery
04-9270	20	Pulmicort Respules 0.5 mg	Pneumonia	Severe	Complete recovery
04-9057	26	Pulmicort Respules	Moniliasis	Severe	Not reported
04-9057	55	Pulmicort Respules	Cramps of arms and legs	Moderate	Complete recovery
04-9057	60	Pulmicort Respules	Coughing	Not reported	Not reported

10.3.3 HPA-Axis Suppression

Four completed non-U.S. supportive clinical study assessing the HPA-axis function of Pulmicort Respules were included in the ISS of NDA. In this section, only Study 04-2188, for which detailed data were available, is reviewed.

10.3.3.1 Budesonide Suspension for Nebulization in Children with Asthma (Study 04-2188)

See Sections 8.5.2.1-4 for details.

Eighteen asthmatic patients aged between 6 and 15 years (mean = 10.7 years) were enrolled into the study to evaluate the safety and efficacy of three doses of budesonide nebulizing suspension (0.5, 1.0, 2.0 mg BID) and to establish the effect relationship with budesonide pMDI connected to a [redacted] spacer. The budesonide nebulizing suspension was administered in a randomized, double-blind, and cross-over fashion. Each dose was used for 4 weeks. There was a run-in period of 2 weeks before a child was randomized. The study ended with a 4-week open period with Pulmicort pMDI (0.2 mg BID) with Nebuhaler as a reference period. Urine samples were collected during the last two days of each treatment period for the standardized 24-hour urinary free cortisol excretion (Urine cortisol/Urine creatinine) measurement. The data showed that there was a statistically significant dose response ($p<0.01$) in urinary cortisol excretion, showing that higher doses gave reduced urinary free cortisol. The two highest doses of budesonide nebulizing suspension (2.0 and 4.0 mg/day) statistically significantly reduced

(43-52%) the excretion of 24 hour urinary free cortisol (creatinine normalized) compared with the run-in period. [88:1-2, 28, 33, 56]

10.4 Post-Marketing Experience

[88:266-8]

The sponsor provided data of post-marketing experience in ISS of NDA. Pulmicort Respules has been approved in 34 countries as of April 16, 1997. It has been estimated that from the time the product was first marketed in 1990 until March 31, 1997, there have been [redacted] patient treatment days post-marketing experience with Pulmicort Respules. Overall, the number of adverse events reported was low. A total of 109 post-marketing adverse event reports for Pulmicort Respules have been received at Astra Draco as of April 16, 1997. No deaths were reported. Of the adverse events that were reported, at least 3 were judged by the reporter as having suspected causality, including immediate and delayed hypersensitivity reactions (e.g., bronchospasm, rash, and dermatitis), glucocorticoids increased (i.e., hypercorticisim), dyspnea, dysphonia, headache, diarrhea, and hyperkinesia.

10.4.1 Spontaneous Reports

[136:33-43]

Spontaneous reports represent post-marketing safety data received by Astra and its licensees as well as cases reported in the scientific literature. A total of 85 reports including 17 serious adverse events were included. The most frequently reported symptoms were bronchospasm (9 reports), dyspnea (6 reports), and rash (6 reports). Of the 17 serious adverse event reports, 4 were bronchospasm, and the remaining were single case reports of the following: collapse NOS, allergic reaction, chest pain, meningitis, adrenal insufficiency, melaena, osteoporosis, superinfection, dyspnoea, asthma aggravated, rash, nephritis interstitial, and corneal ulceration.

10.4.2 National Adverse Drug Reaction Advisory Committee (ADRAC) Reports

[136:93-5]

These were adverse event reports that are provided by national health authorities of some countries to the local Astra marketing company and then forwarded to Sweden by the marketing companies. A total of 24 reports including 4 serious adverse events were included. The most frequently reported adverse events were bronchospasm (4 reports), headache (2 reports), and rash (2 reports). The four serious adverse events reported were polymyositis, extrasystoles, aspergillosis, and bronchospasm aggravated.

10.5 Conclusions and Comments

The safety data resulting from three completed U.S. pivotal, randomized, controlled, double-blind studies (12 weeks) and one completed controlled open-label study (1 year) in pediatric asthma patients aged 6 months to 8 years demonstrated the following:

- In general, administration of Pulmicort Respules in doses of 0.25, 0.5, and 1.0 mg, QD or BID for the treatment of persistent asthma in pediatric patients was well tolerated for a period of 12 weeks. Titrated to patients' symptoms, a daily dose up to 1.0 mg was also generally well tolerated for a period of 52 weeks in patients aged between 4 and 8 years.
- The incidence of serious adverse events was similar between the Pulmicort Respules (2%) and

placebo (3%) groups in 12-week studies. In the 52-week study, the incidence was higher in the Pulmicort Respules group (8%) than the placebo group (4%). The investigators judged all these serious adverse events (except one case of laryngismus) to be unlikely to be related to study treatment, and all the events resolved without sequelae. The most common serious adverse event was bronchospasm.

- In the end of 12-week studies, the proportion of patients with a positive oral fungal culture was higher in the Pulmicort Respules group compared to the placebo group (Section 10.2.1.9). In the 52-week study, the incidence of clinically significant changes in oral cavity fungal cultures in the Pulmicort Respules groups (5%) was also higher than that of the conventional asthma therapy group (2%) (Section 8.4.4.5.6). These results were not unexpected.
- Among Pulmicort Respules groups, the incidences of respiratory infection, bronchitis, ear infection (not otherwise specified), anorexia, and increased alkaline phosphatase were higher in patients aged 6 months to 2 years compared to patients aged between 2 and 4 years as well as 4 and 8 years (Section 10.2.1.4.3). Among patients aged 6 months to 2 years, these adverse events were more frequent in the Pulmicort Respules group compared to the placebo group.

Review of the data provided by the sponsor in the ISS of NDA also revealed several safety issues of concern:

- In both 12-week and 52-week studies, the data of HPA-axis evaluation suggest a measurable systemic effect of Pulmicort Respules (Sections 10.2.1.10 & 10.2.2). It appeared that patients aged 6 months to 2 years are more susceptible to HPA-axis suppression by Pulmicort Respules. In the Pulmicort Respules group, 14% of patients who had normal responsiveness in ACTH-stimulated cortisol levels at baseline showed abnormal responsiveness at Week 52 as compared to 0% in the conventional asthma therapy group. In addition, a statistically significant dose-dependent suppression of urinary free cortisol excretion was noted in Study 04-2188 (Section 10.3.3.1). Pulmicort Respules at doses of 0.5, 1.0 and 2.0 mg BID reduced (32-52%) the excretion of 24 hour urinary free cortisol (creatinine normalized) compared with the run-in period.
- Among the patients who completed the 52-week study, the mean measured growth velocity of patients on Pulmicort Respules was significantly smaller (0.84 cm/year) than that of patients on conventional asthma therapy suggesting a possible growth suppression effect by nebulized budesonide nebulizing suspension.
- [redacted]
- Of note, the number of patients younger than 1 year of age in the pivotal studies was very small. In three pivotal studies, only a total of 13 patients younger than 11 months of age and 26 younger than 1 year of age were evaluated [redacted]

- [redacted]

- It should be also noted that a Pari LC-Jet Plus Nebulizer (with face mask or mouthpiece) and a Pari Master compressor were used to delivered Pulmicort Respules in all three pivotal studies. No other nebulizing devices have been used in the pivotal studies and the safety of Pulmicort Respules delivered by other devices is uncertain.

11. LABELING REVIEW

The proposed labeling is located at volume 1, pages 2-21 of the original NDA. In this section, "Page #" used is relative to a total of 20 pages of the proposed labeling, i.e., the first and last pages of the proposed labeling as Page 1 and 20, respectively.

[redacted]

4. Page 4, lines 17-20: "Budesonide administered via Turbuhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, exercise and adenosine monophosphate) to decrease

Comments: This statement in Pulmicort Turbuhalor package insert does not contain and therefore should be deleted, since these data were not developed with this product or included in this submission.

5.

Comments: This statement, which is based on data from two non-U.S. supportive studies (04-2151 and 04-2270), should be deleted. In Study 04-2151, there was no placebo-control treatment period. The observed improvements in some efficacy variables during treatment periods with Pulmicort Respules could be solely due to natural reversibility of the disease. In the report of Study 04-2270, the sponsor concluded that the study design was faulty. See Sections 8.5.3-8.5.4.4 for details.

6.

Comments: To accurately reflect the data, the statement should be changed to

7.

Comments: 1. Among children who completed the 52-week study, the mean growth velocity of children on Pulmicort Respules was 0.84 cm/year lower compared to children on conventional asthma therapy. This result was statistically significant . (Section 8.4.4.5.7) The sponsor should modify the statement to accurately reflect the data. 2. The pending recommendations from Pulmonary-Allergy Drugs Advisory Committee will be taken into consideration for the final comments.

8.

Comments: 1. In three U.S. pivotal studies, Pulmicort Respules 1.0 mg twice daily was not evaluated in patients younger than 4 years of age. (Table 9.2.1.1) 2. Pulmicort Respules at a dose of 0.25 mg once daily to 1.0 mg twice daily did not improve all primary and secondary endpoints. (Tables 9.2.1.4.1.1 and 9.2.1.4.2) The statement gives readers a wrong impression that Pulmicort

Respules significantly improves all these parameters. 3. The sponsor should modify the statement to accurately reflect the data.

9. Page 5, lines 35-38: [redacted] to 8 years with mild to moderate persistent asthma [redacted] nighttime asthma symptom scores ranged from [redacted]

Comments: To accurately reflect the data, "[redacted] nighttime asthma symptom scores ranged from [redacted]" should be changed to "(mean baseline nighttime asthma symptom scores of treatment groups ranged from [redacted]." (Table 8.2.4.2.1) The baseline nighttime asthma symptom scores ranged from 0 to 3 among patients. [38:130] A similar change should be made to [redacted]

10. [redacted]

Comments: Compared to placebo, significant improvements in FEV_1 and evening PEF were only observed in Pulmicort Respules 0.5 mg and 0.25mg twice daily groups, respectively. The sponsor should delete or modify the statement to more accurately reflect the data.

11. [redacted]

Comments: Between Pulmicort Respules and placebo patients, the difference in the improvement of daytime asthma symptoms was significant, but not in the improvement of nighttime asthma symptoms or the dose of theophylline. (Section 8.5.1.4.1) The sponsor should modify the statement to accurately reflect the data.

12. Page 7, lines 33-40: "[redacted] nighttime asthma symptom scores ranged from 1.13 to [redacted], approximately 70% [redacted] were not previously receiving inhaled corticosteroids. [redacted] significantly improved nighttime asthma symptoms compared with placebo (see figure below). Similar improvements were [redacted]

Comments: Compared to placebo, Pulmicort Respules at 0.25 mg once daily did not significantly improve nighttime asthma symptoms. (Table 8.1.4.4.1.1) The sponsor should modify the statement to accurately reflect the data.

13. [redacted]. "Adverse Events with ≥3% Incidence Reported by Patients on PULMICORT RESPULES" table and "The table above shows all adverse events with an incidence of 3% or more in at least one [redacted] where the incidence was higher with PULMICORT RESPULES than placebo. [redacted]

Comments: The adverse events with an incidence of 3% or more in at least one Pulmicort Respules group where the incidence was equal to or less than that of the placebo group were not included in this table or listed in the labeling elsewhere. These adverse events including sinusitis,

pharyngitis, bronchospasm, bronchitis, otitis media and rash should be listed in the labeling. [134:47]

14. [redacted]

Comments: Incidences of stridor (4%), flu-like disorder (4%), external ear infection (4%), epistaxis (4%), and injection site reaction (4%) were more than twofold in the 2.0 mg Pulmicort Respules daily dose group than the placebo group. [134:46-7] In addition, statistical testing of safety endpoints is not informative as trials were not powered or controlled for such inferential statistics. This statement should be removed.

15. [redacted] **Incidence 1% to ≤3% (by body system):** The information below includes all adverse events with an incidence of 1- ≤3% [redacted] Body as a whole ..."

Comments: 1. In both places, "≤3%" should be changed to [redacted]. 2. [redacted] should be included in the list. [135:56] 3. [redacted] should be listed under [redacted]. [135:59] 3. [redacted]

16. [redacted]

Comments: [redacted]

17. [redacted] adverse events reported in the published literature [redacted] or inhaled budesonide: immediate and delayed hypersensitivity reactions .....; psychiatric symptoms ..."

Comments: Several cases of bone disorder including avascular necrosis of the femoral head and osteoporosis have been reported in patients using nasal or inhaled budesonide. This observation should be incorporated in the statement.

18. [redacted] PULMICORT RESPULES should be administered with a jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. Ultrasonic nebulizers are not suitable for the adequate administration of PULMICORT RESPULES and therefore are not recommended."

Comments: A statement should be made, depicting that a Pari LC-Jet Plus Nebulizer (with face mask or mouthpiece) connected to a Pari Master compressor was used to deliver Pulmicort Respules to each patient in 3 U.S. pivotal studies and the safety and efficacy of Pulmicort Respules delivered by other nebulizers and compressors have not been established.

12. STUDY AUDIT

Based primarily on the degree of improvements in the primary efficacy endpoints and the number of patients studied, four investigators participating the U.S. pivotal studies were selected for audit conducted by the Division of Scientific Investigations (DSI). These investigators are [redacted]

No substantial departures from pertinent federal regulations or good clinical investigational practice were found. The preliminary review does not reveal any objectionable conditions which would preclude the use of the data submitted in support of the pending NDA.

13. CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted three 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group U.S. studies (Studies 04-3069, 04-3072, and 04-3100) as primary evidence to support the efficacy and safety of Pulmicort Respules (budesonide nebulizing suspension) in pediatric asthma patients aged [redacted] to 8 years. In addition, the sponsor also submitted one randomized, active-controlled, open-label, long-term U.S. study (Study 04-3069B), which was a 52-week extension of Study 04-3069, to support the safety of Pulmicort Respules in pediatric asthma patients.

In general, the data demonstrated that administration of Pulmicort Respules in doses of 0.25, 0.5, and 1.0 mg, once daily and/or twice daily resulted in improvements in most of the primary (nighttime and daytime asthma symptom scores) and secondary endpoints (FEV_1, FVC, PEF, $FEF_{25-75\%}$, use of breakthrough medication, proportion of patient discontiuations from the study, etc.) compared to placebo. These improvements were not consistently statistically significant. The improvements in efficacy endpoints were more consistent in patients on Pulmicort Respules twice daily than those on Pulmicort Respules once daily. After adjusting for multiple comparisons with Dunnett's test, 4 of 10 once daily dosing groups and 9 of 10 twice daily dosing groups maintained statistically significantly greater improvements in primary endpoints compared to the placebo. For secondary endpoints, 11 of 35 once daily dosing groups and 22 of 35 twice daily dosing groups demonstrated statistically significantly greater improvements compared to placebo. The improvements in patients treated with Pulmicort Respules 0.5 mg twice daily yielded most consistent improvements. At the doses used, there was no dose-reponse improvement in any efficacy endpoint. The onset of improvement in asthma symptoms can occur within 2 to 4 days of beginning treatment, although maximum benefit may not be achieved for 4 to 6 weeks, or longer. The improvements in primary endpoints by Pulmicort Respules appeared less consistent in Black and Hispanic patients compared to Caucasian patients. In this regard, 5 of 12 Black dose groups and 3 of 12 of Hispanic dose groups failed to demonstrate numerical improvements in asthma symptom scores compared to placebo.

Administration of Pulmicort Respules suspension in doses of 0.25, 0.5, [redacted] once daily and/or twice daily for the treatment of asthma in patients aged [redacted] to 8 years was generally well tolerated for a period of 12 weeks. Titrated to patients' symptoms, a daily dose up to 1.0 mg

was also generally well tolerated for a period of 52 weeks. The incidence of serious adverse events was similar between the Pulmicort Respules (2%) and placebo (3%) groups in 12-week studies. In the 52-week study, the incidence was higher in the Pulmicort Respules group (8%) than the placebo group (4%).

The safety data suggested a possible dose-dependent HPA-axis suppression by Pulmicort Respules. In the 52-week study, the adjusted mean change from baseline in ACTH-stimulated cortisol levels was -22.3 nmol/L in the Pulmicort Respules group compared to 39.1 nmol/L in the conventional asthma therapy group. In the Pulmicort Respules group, 14% of patients who had normal responsiveness in ACTH-stimulated cortisol levels at baseline showed abnormal responsiveness at Week 52 as compared to 0% in the conventional asthma therapy group. A statistically significant dose-dependent suppression of urinary free cortisol excretion was noted in patients aged between 6 and 15 years in a non-U.S. supportive study (04-2188). Pulmicort Respules at doses of 0.5, 1.0 and 2.0 mg, twice daily reduced (32, 43, and 52%, respectively) the excretion of 24 hour urinary free cortisol (creatinine normalized) compared with the run-in period. When the data of three U.S. 12-week primary studies are combined and stratified by age, the adjusted mean changes from baseline in ACTH-stimulated cortisol levels were -35.9, -144, and -19.4 nmol/L, respectively in the Pulmicort Respules 0.25, 0.5, and 1.0 mg total daily dose groups compared to 89.8 nmol/L in the conventional therapy group in patients aged between 6 months and 2 years.

The safety data also suggested that administration of Pulmicort Respules suspension at total daily dose up to 1 mg might be associated with a decrease in growth velocity in pediatric patients. Among children who completed the 52-week study, the mean growth velocity of children on Pulmicort Respules was 0.84 cm/year lower than that of children on conventional asthma therapy ($p<0.05$).

[redacted]

APPEARS THIS WAY
ON ORIGINAL