6.2.2.3.1 *Adverse Events by Gender*

[8/7/1998; 8:68-70, 9:36-9]

Without taking the increased average duration of exposure for the Pulmicort Respules patients into account, the reported incidences for most AEs in either gender appeared higher in the Pulmicort Respules group. After adjusting for the length of time in the study, the incidences of reported AEs in the two treatment groups were not significantly different.

The AE(s) with an incidence of ≥3% and a relative risk >2 (the Pulmicort Respules group versus the conventional therapy group) in the Pulmicort Respules group was eczema for male patients and were flu-like disorder, earache, purpura, moniliasis, eye infection NOS, and lymphadenopathy for female patients.

6.2.2.3.2 *Adverse Events by Age*

[8/7/1998; 8:70-4, 9:61-6]

Without taking the increased average duration of exposure for the Pulmicort Respules patients into account, the reported incidences for most AEs in each age range appeared higher in the Pulmicort Respules group. After adjusting for the length of time in the study, the incidences of reported AEs in the two treatment groups were not statistically significantly different except rhinitis which occurred more frequently in patients aged ≥2 - <4 years and on Pulmicort Respules.

No apparent age effect on the incidences was found in most AEs. Adverse events, which occurred most frequently in Pulmicort Repules patients aged ≥1 - <2 years and more frequently in the Pulmicort Repules group than placebo in all age ranges suggesting an age effect, included bronchitis, ear or hearing symptoms NOS, moniliasis, gastroenteritis, fever, eczema, and increased alkaline phosphatase. [8/7/1998; 8:71-4]

For each age range, the AEs with an incidence of ≥3% and a relative risk >2 in the Pulmicort Respules group were as the following: flu-like disorder, vomiting, nervousness, varicella, and pneumonia for patients aged aged ≥1 - <2 years; allergy, flu-like disorder, pain, diarrhea, ear or hearing symptoms NOS, earache, bronchitis, dyspnea, and rhinitis (statistically different between the 2 treatment groups) for patients ≥2 - <4 years; earache and moniliasis for patients ≥4 years. [8/7/1998; 9:61-6]

6.2.2.4 Serious Adverse Events

[8/7/1998; 8:89-114]

No deaths were reported in the three U.S. long-term open-label studies. A total of 55 patients experienced 63 SAEs (Original Review: Section 8.4.4.5.2.4; Current Review: Sections 5.1-2.4.5.2.4). The incidence of serious adverse events was similar between the Pulmicort Respules (8.3%) and placebo (8.1%) groups. The most common SAE was bronchospasm (n=32). All SAEs were judged by the investigator to be unlikely caused by the treatment. One SAE (bronchospasm) could be classified to be "possibly" caused by the treatment in a patient receiving Pulmicort Respules.

6.2.2.5 Oropharyngeal Fungal Cultures

[8/7/1998; 8:170-1]

The incidence of positive oral fungal culture increased slightly from Baseline (42.7%) to Week 52 (43.6%) in the Pulmicort Respules group. In contrast, the incidence decreased from Baseline (46.3%) to Week 52 (35.7%) in the conventional therapy group. A total of 22 patients including 18 (4.1%) in the Pulmicort Respules group and 4 (1.8%) in the conventional therapy group experiencing clinically relevant fungal infections considered to be AEs. The causal link between the study drug and fungal culture AEs was judged by the investigator as possible or probable in 15 patients in the Pulmicort Respules group and 3 patients in the conventional therapy group. This finding is not unexpected and consistent with clinical observation that the incidence of oral moniliasis is increased in patients using inhaled steroids.

Table 6.2.2.5. Oral Fungal Culture Results. Data are Pooled from the Three U.S. Open-Label Pulmicort Respules Clinical Studies Excluding Missing Cases.

	Baseline		Week 52	
	Convetional Asthma Therapy (n=218)	Pulmicort Respules (n=438)	Convetional Asthma Therapy (n=171)	Pulmicort Respules (n=399)
No Growth	117 (54%)	251 (57%)	110 (64%)	225 (56%)
Growth	101 (46%)	187 (43%)	61 (36%)	174 (44%)
Minimum Growth	30 (14%)	54 (12%)	18 (11%)	42 (11%)
Moderate Growth	24 (11%)	59 (13%)	21 (12%)	35 (9%)
Heavy Growth	47 (22%)	74 (17%)	22 (13%)	97 (24%)

Data Source: [8/7/1998; 9:159]

6.2.2.6 HPA-Axis Suppression

[8/7/1998; 8:164-6]

In Studies 04-3072B and 04-3100B, the conventional asthma treatments included inhaled steroids; in Study 04-3069B, it did not include inhaled steroids. With one exception (i.e., the conventional therapy group in Study 04-3069B), the mean increase in cortisol levels after ACTH-stimulation at Week 52 was less than that at baseline for both treatment groups in these studies, suggesting a measurable HPA-axis suppression of inhaled steroids in both groups. (Table 6.2.2.6A) The combined data of all 3 studies demonstrated that the adjusted mean changes in ACTH-stimulated cortisol levels from baseline to Week 52 were numerically more negative in patients on Pulmicort Respules compared to those on conventional therapy. In addition, the percentage of patients with shifts in ACTH-stimulated cortisol levels from normal to abnormal after one year of treatment in patients on Pulmicort Respules (24%) was slightly higher than those on conventional therapy (21%). (Table 6.2.2.6B) Further, all 7 patients in the conventional therapy group, whose ACTH stimulation tests were abnormal at baseline, reverted to normal by 52 weeks. Only 8 of 14 did so in the Pulmicort Respules group. These data suggest that patients on Pulmicort Respules had more HPA-axis suppression than those on conventional therapy.

Table 6.2.2.6A. Summary Results of Adjusted Mean Changes in ACTH-stimulated Cortisol Levels from Baseline for Patients Who Completed One year of Open-label Treatment. Data Are Pooled from the Three 52-Week U.S. Open-Label Studies.

Study	Adjusted Mean Changes in ACTH-stimulated Cortisol Levels from Baseline (nmol/L)		p-value[1]
	Conventional Therapy	Budesonide Respules	
04-3069B	39.1	-22.3	0.293
04-3072B	-115.0	-96.2	0.772
04-3100B	-53.0	-99.7	0.278
All	-67.7	-98.4	0.312

[1] Budesonide Repules group vs. conventional therapy group

Data source: (Original Review: Table 8.4.4.5.3A; Current Review: Tables 5.1-2.4.5.3A); [8/7/1998; 8:165].

Table 6.2.2.6B: Shifts in ACTH-Stimulation Test From Baseline (Last Double-Blind Observation) to Last Observation in Open-Label for Patients Who Completed One Year of Open-Label Treatment. Data Are Pooled from the Three U.S. Open-Label Studies.

ACTH Stimulation Test[2]	Baseline	Open-Label Treatment			
		Conventional Asthma Therapy (N=55)[1]		Pulmicort Respules (N=122)[1]	
		Abnormal	Normal	Abnormal	Normal
All Patients	Abnormal	0 (0%)	7 (100%)	6 (43%)	8 (57%)
	Normal	10 (21%)	38 (79%)	26 (24%)	82 (76%)

Data Source: [8/7/1998; 9:157].

1. Total n for each treatment group was based on patients with non-missing ACTH and basal cortisol data at baseline and Week 52.
2. Normal adrenal function was defined as basal plasma cortisol >150 nmol/L and either ACTH-stimulated plasma cortisol increased by 200 nmol/L above basal plasma cortisol level or ACTH stimulated plasma cortisol >400 nmol/L after 60 minutes.

6.2.2.7 Long-Term Growth Effect in Children

[8/7/1998; 8:167-9]; (Original Review: Section 8.4.4.5.7; Current Review: Sections 5.1-2.4.5.7)

Given the signal from the ACTH stimulation testing data, one might expect a growth inhibiting effect of Pulmicort Respules, since other data reviewed by the Agency suggest growth inhibition is more sensitive to systemic actions of inhaled or intranasal steroids than is ACTH stimulation testing. Patient characteristics and study designs were slightly different among three long-term open-label studies.

Table 6.2.2.7. Comparison of Patient Characteristics and Study Designs among Three One-Year Open-Label Studies.

	Patient Characteristics and Study Designs		
	04-3069B	04-3072B	04-3100B
Age	6 months - 8 years	4-8 years	6 months - 8 years
Patients Who Use ICS[1] Prior to Double-Blind Phase	0%	100%	30%
Conventional Treatments Included ICS	No	Yes	Yes

[1] ICS = inhaled corticosteroid.

The data of growth velocity in 3 studies are summarized in the following table.

Table 6.2.2.7. Summary of Mean Measured Growth Velocity (cm/year) over One Year (Week 0 to Week 52) for Patients Who Completed One Year of Open-Label Treatment. Data Are Pooled from the Three U.S. Open-Label Studies.

	Mean Measured Growth Velocity (cm/year)		
Study	**04-3069B**	**04-3072B**	**04-3100B**
Budesonide Respules	6.55±2.08 (n=150)	5.68±1.71 (n=47)	6.96±2.34 (n=167)
Conventional Therapy	7.39±2.51 (n=58)	4.97±2.00 (n=25)	6.21±2.43 (n=72)
Budesonide – Conventional	-0.84*	0.71	0.75

Data Source: (Original Review: Table 8.4.4.5.7A; Current Review: Tables 5.1-2.4.5.7A)
* $p<0.05$

There were problems in the assessment of growth velocity in these studies. These included the following: 1. Treatments were not blinded. 2. Baseline growth velocity for an appropriate period of time (e.g. 6 months) was not assessed. 3. Rerandomization between double-blind (12-week) and open-label (52-week) phases without washout period. 4. The use of oral steroids for acute asthma exacerbation. The problems specific for Studies 04-3072B and 04-3100B included the following: 1. Significant proportion of patients had various intervals between the end of double-blind phase and the beginning of open-label phase. 2. The use of inhaled steroids in the conventional therapy group. Thence, these data were hard to interpret, especially for Studies 04-3072B and 04-3100B.

In Study 04-3072B, the proportion of patients who used oral steroids and the average total daily amount used were higher in the conventional therapy group (63% and 1.40 mg/day, respectively) compared to the Pulmicort Respules group (56% and 0.65 mg/day, respectively). In addition, the mean age and height were slightly higher in the conventional therapy group. At baseline, the control of asthma was poorer (higher asthma symptom scores, slightly worse pulmonary function, and higher number of days of breakthrough medication use) in the conventional therapy group. All these might explain, at least partially, why the mean measured growth velocity was smaller in the conventional therapy group. (Sections 5.1.4.5.7)

In Study 04-3100B, the dropout rate in children aged two years or less was significantly higher in the conventional therapy group (56.3%) compared to the Pulmicort Respules group (11.2%); this strongly confounds the interpretation of the comparative growth data since the growth rates of younger and older children may differ dramatically. In addition, both the proportion of patients who used oral prednisone and the average total daily amount used in the conventional therapy group were slighter higher compared to the Pulmicort Respules group. All these may explain, at least partially, why the mean measured growth velocity was smaller in the conventional therapy group. (Section 5.2.4.5.7)

In Study 04-3069B, the mean measured growth velocity in the Pulmicort Respules group was significantly lower (0.84 cm/year) than that of the conventional therapy group. Importantly, in Study 04-3069B, patients were not treated with inhaled steroids prior to the double-blind phase and inhaled steroids were not part of conventional asthma therapy as they were in Studies 04-3072B and 04-3100B. In addition, the proportion of patients who used oral steroids as well as the mean and median of total daily amount used were slightly higher in the conventional therapy group (53%, 0.53 and 0.23 mg/day, respectively) compared to the Pulmicort Respules group (46%, 0.47 and 0 mg/day, respectively). (Section 5.1.4.4.1)

Altogether, the data indicate that long-term administration of Pulmicort Respules at a total daily dose up to 1 mg *is likely* to be associated with a decrease in growth velocity in inhaled steroids naïve children, compared to non-steroidal asthma therapy.

6.3 Conclusions and Comments

The assessment of safety data resulting from three completed U.S. pivotal, 12-week, double-blind studies and one completed 52-week, open-label study (04-3069B) in pediatric asthma patients aged 6 months to 8 years was included in the review of original NDA submission. Review of the new safety data included in this NDA resubmission does not reveal significant differences from those in the safety review of the original NDA.

The data of three completed U.S. pivotal 12-week studies (04-3069, 04-3072, 04-3100), excluding patients under one year of age or patients randomized to 1.0 mg BID treatment, demonstrated the following:

- The incidence of AEs was generally comparable between the placebo and Pulmicort Respules group. Among AEs with an incidence of ≥1% in the Pulmicort Respules group, the incidences of rhinitis (10%), coughing (7%), viral infection (4%), moniliasis (4%), gastroenteritis (5%), diarrhea (3%), abdominal pain (3%), epistaxis (3%), flu-like disorder (2%), earache (2%), purpura (2%), eczema (1%), hyperkinesia (1%), and contact dermatitis (1%) were higher in the Pulmicort Respules group.

The data of three completed U.S. 52-week, open-label studies (04-3069B, 04-3072B, 04-3100B) demonstrated the following:

- Pulmicort Respules at total daily doses of 0 to 1.0 mg was generally well tolerated for a period of 52 weeks in patients aged 1-8 years.
- Only 4 patients aged <1 year were in the Pulmicort Respules group.
- Pulmicort Respules at total daily doses of 0 to 2.0 mg was generally well tolerated for a period of 52 weeks in patients aged 4-8 years.
- The most frequently reported adverse events among Pulmicort Respules patients were respiratory infection (58%), sinusitis (33%), fever (28%), otitis media (23%), and pharyngitis (19%). After adjusting for the length of time in the study, the incidences of reported AEs were generally comparable between the Pulmicort Respules and conventional asthma therapy groups.

Earache was the only AE with a relative risk >2 (the Pulmicort Respules group versus the conventional therapy group) in the Pulmicort Respules group.

- The percentage of patients with reported serious adverse events was similar between the Pulmicort Respules (8.3%) and conventional asthma therapy (8.1%) groups.
- The percentage of patients who discontinued from treatment because of clinical adverse events was similar between the Pulmicort Respules (0.7%) and conventional asthma therapy (0.4%) groups.
- The percentage of patients experiencing clinically relevant fungal infections considered to be AEs was higher in the Pulmicort Respules group (4.1%) compared to the conventional therapy group (1.8%).
- A measurable HPA-axis suppression was observed in both treatment groups and patients on Pulmicort Respules had more HPA-axis suppression than those on conventional therapy.
- Although there were problems making it difficulty to interpret the results of 3 growth studies, the data indicate that long-term administration of Pulmicort Respules at a total daily dose up to 1 mg is likely to be associated with a decrease in growth velocity in inhaled steroids naïve asthmatic children, compared to non-steroidal asthma therapy.

7. LABELING REVIEW

In this section each "Page #" refers to a page number in volume 2 of the NDA resubmission.

[redacted]

studies, suggesting a measurable HPA-axis suppression of inhaled steroids in both groups. (Table 6.2.2.6A) 2. The combined data of all 3 studies demonstrated that the adjusted mean changes in ACTH-stimulated cortisol levels from baseline to Week 52 were numerically more negative in patients on Pulmicort Respules compared to those on conventional therapy. In addition, the percentage of patients with a shift in ACTH stimulation test from normal at baseline to abnormal at Week 52 was slightly higher (24%) in patients on Pulmicort Respules than those on conventional therapy (21%). (Table 6.2.2.6B) Further, all 7 patients in the conventional therapy group, whose ACTH stimulation tests were abnormal at baseline, reverted to normal by 52 weeks. Only 8 of 14 did so in the Pulmicort Respules group. 3. These data suggest that patients on Pulmicort Respules had more HPA-axis suppression than those on conventional therapy. 4. The sponsor should modify the statement to accurately reflect the data.

- [redacted]

Comments: 1. Significant decrease in nighttime and daytime asthma symptoms or reduction in the need for bronchodilator therapy was not observed in all studies with all dosing regimens. (Original Review: Tables 9.2.1.4.1.1 and 9.2.1.4.2) 2. Symptom reduction in response to Pulmicort Respules did not occur across race. It was not consistently observed in Blacks and Hispanics. (Original Review: Table 9.2.1.4.1.4C) 3. For Pulmicort Respules 1.0 mg once daily, a significant improvement in FEV_1 or morning PEF was only seen in 1 of 2 studies. 4. These statements should be modified to accurately reflect the data. 5. The data of 1.0 mg twice daily should not be included since the sponsor is not seeking for the approval of this dosing regimen.

- [redacted] ediatric patients age[redacted] to 8 years with mild to moderate persistent asthma (baseline nighttime asthma symptom scores ranged from [redacted]

Comments: To accurately reflect the data, "(baseline nighttime asthma symptom scores ranged from [redacted]" should be changed to "(mean baseline nighttime asthma symptom scores of the treatment groups ranged from [redacted]" (Original Review: 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]

- [redacted] mean baseline dose of beclomethasone dipropionate 265 mcg/day; [redacted] 0 to 1200 mcg/day"

Comments: This statement should be changed to "mean baseline dose of beclomethasone dipropionate 265 mcg/day, [redacted] 200 to 1200 mcg/day".

- [redacted]

- [redacted]

Comments: This should be changed to "inhaled corticosteroid".

- [redacted]

Comments: 1. These statements should be deleted. 2. In Studies 04-3072B and 04-3100B, many problems in the assessment of growth velocity significantly confound the interpretation of comparative growth data. Study 04-3069B demonstrated that administration of Pulmicort Respules at total daily dose up to 1 mg for one year was associated with a statistically significant decrease (0.84 cm/year) in growth velocity in inhaled steroids naïve asthmatic children, compared to non-steroidal asthma therapy (Section 6.2.2.7); this should be stated in the labeling. 3. A report of the quoted study (AM J Respir Crit Care Med 1998;157:178-183) has not been submitted for review and the data of this study should not be included in the labeling.

[redacted]

Comments: 1. The statements should be modified to indicate that, in many patients, conventional therapy included inhaled steroids other than Pulmicort Respules. A similar change should be made to [redacted] The first sentence should be modified since Studies 04-3072B and 04-3100B will be no longer cited in the previous section.

- [redacted] "**Pediatric Use** ....."

Comments: 1. Immediately after **Pediatric Use** the following class labeling for the orally inhaled corticosteroid drug products should be inserted: "Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis

suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with —— inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with —— inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving —— inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (e.g. via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained ——— To minimize the systemic effects of —— inhaled corticosteroids, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose." 2. The statements in lines 29-36 should be deleted.

- ——— **"ADVERSE REACTIONS ....."**

Comments: The following class labeling for the orally inhaled corticosteroid drug products should be inserted into this section: "Cases of growth suppression have been reported for ——inhaled corticosteroids including ——— (see **PRECAUTIONS, Pediatric Use** section)."

- ——— Adverse Events with ≥3% Incidence Reported by Patients on PULMICORT RESPULES" table.

Comments: Adverse events listed on the table are those with an incidence of 3% or more in at least one Pulmicort Respules group where the incidence was higher than that in the placebo group. The table title should be modified accordingly.

- ——— "The following adverse events occurred 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: sinusitis, pain, pharyngitis, bronchospasm, bronchitis, and headache."

Comments: Fever should be included in the list. [Table 6.2.1.1]

- ——— "The information below includes all adverse events with an incidence of 1 to ≤ 3%, in Pulmicort Respules-treated patients where the incidence was higher with Pulmicort Respules than placebo, ———

Comments: Adverse events listed in this section are those with an incidence of 1 to ≤3% in at least one Pulmicort Respules group where the incidence was higher than that in the placebo group. This sentence should be modified accordingly.

- ———

Comments: This statement should be change to ' ———

- Page 19, line 35 - Page 20, lines 7: "The recommended starting dose and highest recommended dose of PULMICORT RESPULES, based on prior asthma therapy, are listed in the following table.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone		0.5 mg total daily dose
Inhaled Corticosteroids		mg total daily dose
Oral Corticosteroids		mg total daily dose

"

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3. CONCLUSIONS AND RECOMMENDATIONS

The main new clinical data in this NDA resubmission and the information amendment to IND 44,535 are provided in final reports of two multicenter, randomized, open-label, 52-week studies (04-3072B and 04-3100B). The safety data of three pivotal, 12-week studies (04-3069, 04-3072, and 04-3100) excluding patients under one year of age or patients randomized to 1.0 mg BID treatment are included in the updated Integrated Summary of Safety.

Overall, the new data provided in this submission do not raise new safety or efficacy concerns other than those mentioned in the review of original NDA. The safety data of three pivotal studies excluding patients under one year of age or those randomized to 1.0 mg BID treatment are similar to that including these patients. The data of three completed U.S. long-term, open-label studies (04-3069B, 04-3072B, 04-3100B) demonstrated the following: Pulmicort Respules at total daily doses of 0 to 1.0 mg was generally well tolerated for a period of 52 weeks in patients aged 1-8 years. 2. A measurable HPA-axis suppression was observed in both treatment groups and patients on Pulmicort Respules had more HPA-axis suppression than those on conventional therapy (including inhaled steroids other than Pulmicort Respules). 3. Study 04-3069B demonstrated that administration of Pulmicort Respules at total daily dose up to 1 mg for one year was associated with a statistically significant decrease (0.84 cm/year) in growth velocity in inhaled steroids naïve asthmatic children, compared to the non-steroidal asthma therapy. The significant of growth data in Studies 04-3072B and 04-3100B is uncertain due to problems in the study design and several significant confounding factors.

2/3/99

Team Leader comment:

I agree w/ Dr. Chen's review. These data contained in this submission do not change our previous review conclusions of clinical approvability, however the Sponsor has modified the proposed [redacted] to address our concerns [redacted]. Further, the growth studies submitted do not well address the true effect of this formulation, but it certainly still appears budesonide, like other corticosteroids, may inhibit growth.

/S/

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #:	**N20-929**	**APPLICATION TYPE:**	**NDA**
SPONSOR:	**Astra USA, Inc.**	**PROPRIETARY NAME:**	**Pulmicort Respules**
CATEGORY OF DRUG:	**Corticosteroid**	**USAN / Established Name:**	**Budesonide**
		ROUTE:	**Oral Inhalation**
MEDICAL REVIEWER:	**Shan C. Chu, MD**	**REVIEW DATE:**	**05-05-98**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
11-18-97	11-20-97	Full NDA application	
03-12-98	03-16-98	120-day safety update	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
	NDA 20-233	Rhinocort Nasal Inhaler
	NDA 20-441	Pulmicort Turbuhaler
	NDA 20-746	Rhinocort Aqua Nasal Spray

Overview of Application/Review: 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 ——— 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. These dosing regimens were 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. Of note, the data suggested a decrease in growth velocity and a possible dose-dependent HPA-axis suppression in pediatric patients treated with Pulmicort Respules.

Outstanding Issues: 1. A number of statements in the labeling need to be modified or removed. 2. Several CMC issues have to be resolved.

Recommended Regulatory Action:

New Clinical Studies: _____ **Clinical Hold** _____ **Study May Proceed**

NDAs:

Efficacy / Label Supp.: ___X___ **Approvable** _____ **Not Approvable**

Signed: **Medical Reviewer:** /S/ **Date:** 5/5/98

Medical Team Leader: **Date:** 5/6/98

CC: HFD-570/NDA File
HFD-570/Division File
HFD-570/Chu/Meyer/Elashoff/Vogel

TABLE OF CONTENTS

APPEARS THIS WAY
ON ORIGINAL

1. NOTE TO READERS

Square brackets are used throughout this review to include references to the original NDA volumes and pages as well as subsequent amendments to the original NDA. Parentheses are used to include references to sections, tables, and figures in this review.

2. GLOSSARY OF ABBREVIATIONS USED

ACTH:	adrenocorticotropic hormone;
ADRAC:	Adverse Drug Reaction Advisory Committee;
AE:	adverse event;
ANOVA:	analysis of variance;
APT:	all patients treated;
ATC:	Anatomical Therapeutical Chemical (classification system);
AUC:	area under the curve;
BID:	twice a day;
CI:	confidence interval;
CDER:	Center for Drug Evaluation and Research;
CRA:	clinical research associate;
CRF:	case report form;
CV:	coefficient of variation;
FDA:	Food & Drug Administration (USA);
$FEF_{25-75\%}$ (L/sec):	forced expiratory flow during the middle half of the forced vital capacity (liters per second);
FEV_1 (L):	forced expiratory volume in one second (liters);
FVC (L):	forced vital capacity (liters);
GCS:	glucocorticosteroid;
HPA-axis:	hypothalamic pituitary adrenal-axis;
IRB:	Institutional Review Board;
IND:	Investigational New Drug application;
ISE:	integrated summary of efficacy;
ISS:	integrated summary of safety;
L:	liter;
LVCF:	last value carried forward;
MED:	minimal effective dose;
NIH:	(U.S.) National Institutes of Health;
NDA:	New Drug Application;
NOS:	not otherwise specified;
PEF (L/min):	peak expiratory flow (liters per minute);
PFT:	pulmonary function test;
pMDI:	pressurized metered dose inhaler;
p.r.n.:	as the occasion requires;
p-value:	probability value;
QD:	once a day;
SAE:	serious adverse event;

SD:	standard deviation;
SEM:	standard error of the mean;
WHO:	World Health Organization.

3. CONDUCT OF THE REVIEW

The documents used for this review consists of the following:

1. Medical officer's copy of NDA 20-929 submitted to CDER on November 20, 1997 in 117 volumes, including volumes 1.1, 1.29-1.136, and selected case report forms in volumes 1.224-231.
2. Amendment submitted in one volume on January 7, 1998.
3. Amendment submitted in four volume on February 9, 1998
4. The 120 day-safety update submitted in two volumes on March 16, 1998.

The review of the efficacy and safety of the drug product (Pulmicort Respules, budesonide nebulizing suspension) was started from an overview of the whole NDA by assessing the labeling proposed by the sponsor and surveying all volumes of the medical officer's copy of this NDA. The review of three completed multicenter, randomized, double-blind, placebo-controlled, parallel-group studies was then started. The study containing the highest number of patients (Study 04-3100) was reviewed first, followed by Study 04-3069, and then Study 04-3072 containing the lowest number of patients. Next, Study 04-3069B, a randomized, active-controlled, open-label, 52-week extension of Study 04-3069, was reviewed.

Upon completion of the review of the individual studies, an integrated summary of efficacy and of safety were compiled and an overall assessment of the NDA was concluded and recommendations made. In general, the sponsor's reports provided the basis for reviewing each individual clinical study as well as the integrated summaries.

Most of the tables and figures in this review were taken from the sponsor's report, many with modification. Some tables were made using the data from tabulations in the NDA. A few tables were created by working jointly with the statistician, Barbara Elashoff.

Table 3: Design Features of the U.S. Pivotal Studies.

Study	Control	Pulmicort	Treatment	Patient Population		
		Respules Dose	Duration	Age (years)	# of Patients randomized	Inhalaed Steroid[1]
04-3069	Placebo	0.25 mg QD 0.5 mg QD 1.0 mg QD	12 weeks	6 months to 8 years	359	Naive
04-3072	Placebo	0.25 mg BID 0.5 mg BID 1.0 mg BID	12 weeks	4 to 8 years	178	Dependent
04-3100	Placebo	0.25 mg QD 0.25 mg BID 0.5 mg BID 1.0 mg QD	12 weeks	6 months to 8 years	481	Optional
04-3069B[2]	Conventional therapy	0 - 1.0 mg QD or QOD	52 weeks	6 months to 8 years[3]	272	Dependent [3]

[1] Prior to randomization.
[2] Study 04-3069B was a 52-week extension of Study 04-3069.
[3] Age and status of inhaled steroid shown here are not the data on the day of randomization in Study 04-3069B. They are the same as those in Study 04-3069.

4. BACKGROUND

Budesonide is a corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In U.S, budesonide in different formulations has been approved for the treatment of allergic rhinitis (Rhinocort Nasal Inhaler) and for the treatment of asthma (Pulmicort Turbuler) in patients 6 years or older. In this NDA, the sponsor is seeking approval of Pulmicort Respules (budesonide nebulizing suspension) for the treatment of asthma in children aged [redacted] to 8 years

4.1 Proposed Indications and Dosage

[1:9, 19-20]

Pulmicort Respules is indicated for the maintenance treatment of asthma and as prophylactic therapy in children aged [redacted] to 8 years. It is also indicated for children aged [redacted] to 8 years with asthma who require systemic corticosteroid administration. [1:9]

The Proposed dosage is detailed in the following table. In symptomatic children (2 years or less) not responding to non-steroidal therapy, a starting dose of 0.25 mg daily of Pulmicort Respules may be considered.

Table 4.1: The Recommended Starting Dose and Highest Recommended Dose. [1:20]

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered as a single or divided dose	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered as a single or divided dose	1.0 mg total daily dose
Oral Corticosteroids	[redacted]	

4.2 Related NDAs

- NDA 20-233: Rhinocort Nasal Inhaler, approval data: February 14, 1994.
- NDA 20-441: Pulmicort Turbuler (dry powder inhaler), approval data: June 24, 1997.
- NDA 20-746: Rhinocort Aqua (aqueous nasal spray), approvable letter date: October 29, 1997.

5. CHEMISTRY, MANUFACTURING, AND CONTROLS

The active component of Pulmicort Respules is budesonide, a corticosteroid designated chemically as (RS)-1β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. [1:2]

Pulmicort Respules is a sterile suspension which should be administered from jet nebulizers. In addition to the active ingredient budesonide, it also contains the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80 and water. [redacted] dose strengths are available in 2 mL respules: 0.25 mg (0.125 mg/mL); 0.5 mg (0.25 mg/mL); [redacted]

6. CLINICAL PHARMACOLOGY

Budesonide is a glucocorticosteroid that exhibits potent glucocorticoid and weak mineralcorticoid activity. The precise mechanism of corticosteroid actions on inflammation in asthma is not well defined although corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types and mediators involved in allergic- and non-allergic-mediated inflammation. The sponsor reports that budesonide has shown anti-inflammatory effects on airway cellular inflammation, normalizing bronchial epithelium by increasing the number of ciliated cells and intraepithelial nerves and decreasing the number of epithelial inflammatory cells, especially eosinophils. These tissue effects have been seen after three months of treatment. [29:114-5]

Pulmicort Respules is designed to be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces. Each nebulizer-compressor combination has its own characteristic drug output and droplet size distribution. [29:118] The delivered dose is determined by these factors in combination with the patient's breathing cycle and inspiratory flow. The deposition within the body is determined by the inspiratory flow, droplet size, size and geometry of the airways, and whether breathing is through the nose or the mouth. The Pari LC Jet Plus with the Pari Master compressor ranked among the highest as assessed by in vitro techniques for respirable mass of the delivered dose and had also among the shortest nebulization times. [25:18-30] This combination was selected for the clinical Phase 3 studies in U.S. and the compementary bioavailability study in asthmatic children (04-3104). In addition to nebulizer, the patient-device interface plays an important role in the efficient use of inhalation devices. A mouthpiece or face mask is the traditional patient-device interface between a nebulizer and the patient. Face masks have been shown to be as efficient patient-device interfaces as mouthpieces. [25:14]

In one study (04-2290), a slight age-dependent increase in the delivered dose expressed as percentages of the labeled Pulmicort Respules in children aged 6 months to 4-7 years using a conventional constant output jet nebulizer (———) with a face mack was found. The delivered doses were 11.5%, 12.1%, and 14.6% of labeled dose in children aged 0.5-1 year, 2-3 years, and 4-7 years. [25:32-4] In the other study (04-3104), the delivered dose was 23% of labeled dose and the systemic (lung + oral) availability following administration of Pulmicort Respules via a Pari LC Jet-Plus nebulizer with a mouthpiece was 6.5 % of the labeled dose and 28% of the delivered dose in asthmatic children aged 3.5-6 years. [29:122] The systemic availability in healthy adults using the same nebulizer/compressor system was approximately 2-3 times higher than in young children.

Systemically, budesonide is rapidly and extensively metabolized in man by liver and then excreted in urine and feces in the form of metabolites. Using in vitro studies with human liver homogenates, two major metabolites formed via cytochrome P450 3A catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound.

7. FOREIGN MARKETING HISTORY

[1:34-43; Amendment, 2/2/98; 120-day safety update, 1:87]

Pulmicort Respules was first approved for the prevention and treatment of bronchial asthma in Finland on March 14, 1990. By December 1997, Pulmicort Respules has been approved for the prevention and treatment of bronchial asthma by 37 countries. In all of these 37 countries, twice daily dosing, but not once daily dosing, has been approved. In more a half of these countries, Pulmicort Respules has been approved for use in children.

Reviewer's Comments: 1. In 4 countries, Pulmicort Respules has been approved for use in infants aged 3-6 months and older. 2. The 1.0 mg twice daily dosing has not been approved as the maintenance dose for children younger than 12 years old in any country. 3. For children aged 12 years and younger, the approved starting dose is 0.5-1 mg twice daily and the approved maintenance dose is 0.25-0.5 mg twice daily in most countries.

Table 7: Countries Where Pulmicort Respules Have Been Approved: Approved Age Range and Dosage for Children.[1]

Country	Approved Age[2]	Starting Dose[2]	Maintenance Dose[2]
Argentina	-	-	-
Australia	N.S.	0.5-1 mg twice daily	0.25-0.5 mg twice daily
Austria	N.S.	N.S.	N.S.
Bahrain	-	-	-
Belgium	≥ 3 months	0.5-1 mg twice daily	0.25-0.5 mg twice daily
Canada	3 months - 12 years	N.S.	N.S.
Colombia	-	-	-
Cyprus	-	-	-
Czech Republic	-	-	-
Denmark	N.S.	N.S.	N.S.
Estonia	-	-	-
Finland	N.S.	N.S.	N.S.
France	N.S.	N.S.	N.S.
Germany	Infants - 12 years	20 drops - 2 ml	10 - 20 drops
Hong Kong	-	-	-
Iceland	≥ 6 months	0.25-0.5 mg twice daily[3]	N.S.
Indonesia	3 months - 12 years	0.5-1 mg twice daily	0.25-0.5 mg twice daily
Ireland	N.S.	0.5-1 mg twice daily	0.25-0.5 mg twice daily
Israel	-	-	-
Korea	-	-	-
Kuwait	-	-	-
Luxemburg	-	-	-
Malaysia	-	-	-
Netherlands	-	-	-
New Zealand	-	-	-
Norway	N.S.	N.S.	N.S.
Peru	-	-	-
Philippines	N.S.	0.5-1 mg twice daily	0.25-0.5 mg twice daily
Portugal	N.S.	0.5-1 mg twice daily	0.25-0.5 mg twice daily
Singapore	N.S.	N.S.	N.S.
South Africa	-	-	-
Spain	N.S.	0.5-1 mg twice daily	0.25-0.5 mg twice daily
Sweden	≥ 6 months	0.25-0.5 mg twice daily[3]	N.S.
Switzerland	N.S.	0.5-1 mg twice daily	N.S.
UAE	-	-	-
Uganda	-	-	-
UK	3-12 years	0.5-1 mg twice daily	0.25-0.5 mg twice daily
	≥ 12 years	0.25-0.5 mg twice daily	0.5-1 mg twice daily

1 In some countries, different names other than Pulmicort Respules are used for marketing.
2 Only the approved age range and dosage for children are shown.
3 Occasionally the dose may be increased to 1 mg twice daily.
–: No information available.
N.S.: Not specified.

8. CLINICAL STUDIES

8.1 Study 04-3100: A Study of Four Dose Regimens of Budesonide (Pulmicort) Nebulizing Suspension and Placebo in Asthmatic Children Aged Eight Years and Younger.

8.1.1 Objectives

[60:14, 34-5]

The objectives of this study were to compare the relative efficacy and safety of four regimens of budesonide nebulizing suspension, 0.25 mg QD, 0.25 mg BID, 0.5 mg BID and 1.0 mg QD, versus placebo BID, in pediatric asthmatic patients aged six months to eight years.

8.1.1.1 Primary Efficacy Variables

Since reliable measurements of lung function are difficult to perform consistently in children below the age of five-to-six years, symptom scores were chosen as the primary efficacy variable.

- The mean change from baseline (mean of the last seven days prior to randomization) in nighttime and daytime asthma symptom scores over the 12-week treatment phase (mean over 12 weeks, Weeks 0-12).

8.1.1.2 Secondary Efficacy Variables

- The number of days breakthrough medication (short-acting inhaled bronchodilator) was used.
- The amount of breakthrough medication (short-acting inhaled bronchodilator) used.
- Spirometry test variables (FEV_1, $FEF_{25-75\%}$ and FVC) performed at clinic visits in the subset of patients capable of performing spirometry testing.
- PEF measured daily in the morning and evening in the subset of patients capable of performing PEFs.
- Proportion of patient discontinuations from the study.
- Treatment failures (defined as worsening of airways symptoms, becoming intolerable or resulting in unacceptable risks to the patient and/or requiring the use of non-permitted asthma medications and/or hospitalization).

8.1.1.3 Safety Variables

- Reported adverse events (AEs).
- Pre- and post-ACTH-stimulation effects on HPA-axis function in a subset of patients.
- Changes in physical examinations (including vital signs, body weight and height) and clinical laboratory tests (including oropharyngeal and/or nasal fungal cultures).

8.1.2 Design

[60:14-8]

This was a multicenter randomized, double-blind, placebo-controlled, parallel-group study. A total of 481 patients from 38 study centers located throughout the USA participated in the study.

Patients initially entered a two-to-three-week baseline phase, which was followed by a 12-week treatment phase. On entry into the study (Visit 1) patients underwent several screening evaluations and were provided with a diary card to record on a daily basis nighttime and daytime asthma symptom scores, daily use of bronchodilator therapy, as well as morning and evening PEFs in the subset of patients capable of performing this test. At the end of the baseline phase (Visit 2) patients who fulfilled the inclusion and exclusion criteria discontinued taking their chronic asthma medications and were randomized to receive one of the following treatments for 12 weeks:

- budesonide nebulizing suspension, 0.25 mg QD in the morning and placebo QD in the evening;
- budesonide nebulizing suspension, 0.25 mg BID, once in the morning and once in the evening;
- budesonide nebulizing suspension, 0.5 mg BID, once in the morning and once in the evening;
- budesonide nebulizing suspension, 1.0 mg QD in the morning and placebo QD in the evening;
- placebo BID, once in the morning and once in the evening.

Patients subsequently returned to the clinic for four additional visits (Visits 3-6) during the treatment phase.

Figure 8.1.2. Design of Study 04-3100. [60:16]

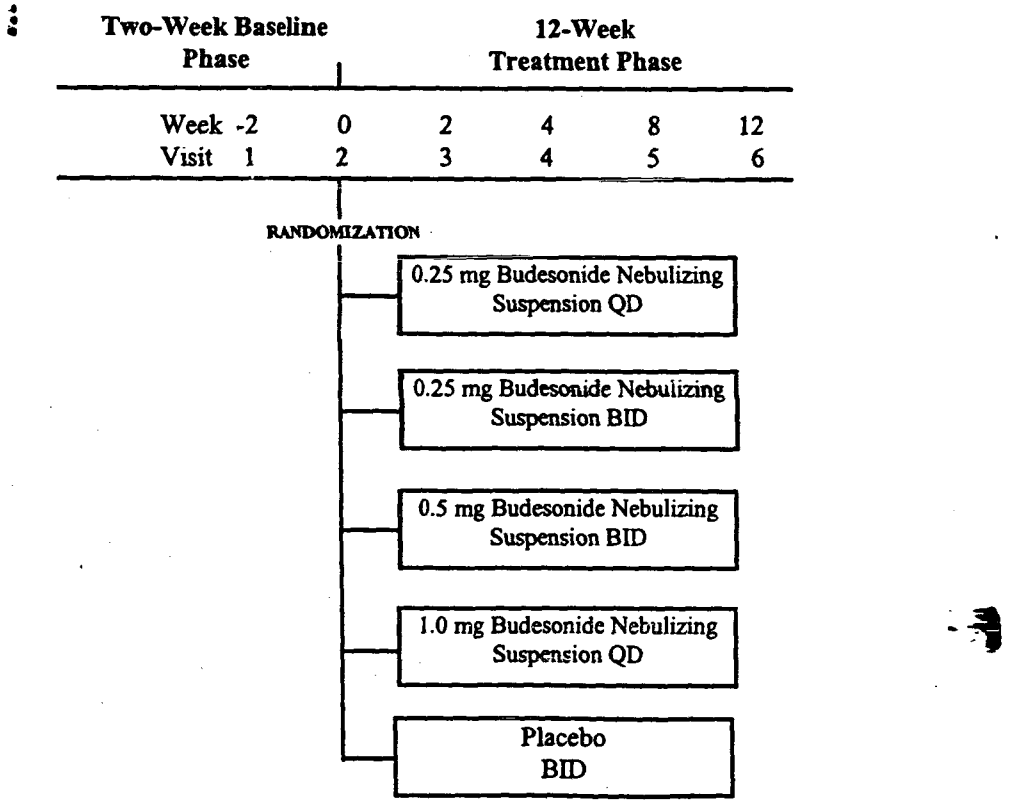

Table 8.1.2. Schedule of Study Procedures. [60:17]

Week Number:	-2	0	2	4	8	12
Visit Number:	1	2	3	4	5	6
Clinical Procedures:						
Informed Consent Form	X					
Check Inclusion/Exclusion Criteria	X	X				
Medical History	X					
Comprehensive Physical Examination; Vital Signs	X					X
Brief Physical Examination with Vital signs		X	X	X	X	
Height, Weight	X	X	X	X	X	X
Spirometry Testing (for patients capable of performing the maneuvers):						
FEV_1, FVC, $FEF_{25-75\%}$	X	X	X	X	X	X
Reversibility (could be met at Visits 1 or 2)	X					
Laboratory Assessments:						
Hematology, Blood Chemistry	X					X
Urinalysis	X					X
Basal & Post-ACTH Plasma Cortisols (selected sites only)	X					X
Oropharyngeal and/or Nasal Fungal Cultures (Repeated as judged necessary by the investigator)		X				X
Other:						
Review Adverse Events	X	X	X	X	X	X
Review Daily Diaries (Asthma Symptoms, Breakthrough Medications, PEF)		X	X	X	X	X
Return Study Drug/Assess Compliance			X	X	X	X
Practice and/or Review Inhalation Technique, PEF Technique, Use/Care of Equipment	X	X	X	X	X	
Dispense Study Drug/Nebulizing Equipment		X	X	X	X	
Dispense New Diaries	X	X	X	X	X	

8.1.3 Protocol

8.1.3.1 Selection of Study Population

[60:18-20]

Patients who fulfilled the inclusion and exclusion criteria given below were eligible for enrollment into the study.

8.1.3.1.1 Inclusion Criteria

1. Male or female outpatients between 6 months and 8 years of age at screening.
2. Diagnosis of asthma as defined by the National Institutes of Health of the U.S. Department of Health and Human Services, including the following symptoms, as judged by the investigator:
   - Exacerbations of cough and/or wheezing on a frequent basis with infrequent severe exacerbations during the last six months.
   - Daily use of at least one chronic asthma medication (which could have included an inhaled corticosteroid) and periodic use of a breakthrough (bronchodilator) medication for at least three months prior to Visit 1. The chronic asthma medication could have been an inhaled corticosteroid. If so, the patient must have had been on the same inhaled corticosteroid for at least two months prior to Visit 1.
3. Patients must have met the following drug restrictions prior to Visit 1:
   - No long-term use of systemic steroids within 12 weeks.
   - No intermittent use of systemic steroids within 30 days.
   - No use of inhaled glucocorticosteroids within 8 hours. [61:6]
   - No long-acting inhaled β_2-agonists within seven days.
   - No astemizole within 90 days.
   - No investigational drugs within 30 days.
   - No ipratropium bromide within 48 hours.
   - No combination preparations of expectorants and/or sedatives with bronchodilators, and over-the-counter asthma medications within 24 hours.
   - Patients on maintenance immunotherapy must have been on a constant dose at least two months prior to Visit 1.
4. Patients old enough to perform consistent PFTs must have had a basal $FEV_1 \geq 50\%$ of predicted and reversibility of $\geq 15\%$ at 15 ± 5 minutes after a standard dose of inhaled bronchodilator. Both criteria could have been met at Visit 2.
5. At Visit 2, the patient had to have demonstrated asthma symptoms (daytime or nighttime; score of 1, 2 or 3) during at least 5 of the last 7 days prior to Visit 2. The baseline phase could have been extended by one week if a patient could not demonstrate asthma symptoms during five out of the last seven days. [60:27]
6. The patients and/or legal guardians must have been willing and able to comply with the protocol procedures, including the correct use of nebulizing equipment and the completion of daily diaries (for asthma symptoms, use of breakthrough medication, and PEF if applicable).
7. The legal guardians must have read, understood and signed the written witnessed Informed Consent Form for the double-blind treatment phase.

8.1.3.1.2 Exclusion Criteria

1. History of severe and/or unstable asthma that, in the judgment of the investigator, may have compromised the health of the patient.

2. History of assisted ventilation, except at birth.
3. Hospitalization for treatment of airway obstruction within 30 days prior to Visit 1.
4. Upper respiratory tract infection with infectious sequelae of the lower respiratory tract within 14 days prior to Visit 1.
5. Diagnosis of other concomitant lung diseases (e.g., cystic fibrosis, bronchopulmonary dysplasia).
6. Clinically relevant baseline laboratory results defining diseases or significant medical conditions which may have put the patient at risk, or that could have influenced the final results of the study, as judged by the investigator.
7. Patient had been scheduled for in-patient hospitalization, including elective surgery under general anesthesia during study phase.
8. Patient required treatment for asthma symptoms only during seasonal allergen exposure, but is free of symptoms and required no treatment at other times. [61:5]
9. Disability or residency in geographical location preventing regular attendance to scheduled visits.
10. Previous participation in any budesonide nebulizing suspension study.

8.1.3.2 Study Drugs

[60:21]

Investigational Drug:	Budesonide (0.125, 0.25, or 0.5 mg/mL) in 2.0 mL nebulizing suspension (containing disodium edetate, sodium chloride, sodium citrate, [redacted] citric acid, Polysorbate 80 and water).
Placebo:	2.0 mL nebulizing solution (as above) without budesonide.
Breakthrough Medication:	Breakthrough medication was defined on an individual basis at Visit 1, and was to be the breakthrough medication used by the patient prior to study enrollment, as long as it was not an excluded one. The breakthrough medication, both delivery and formulation, had to be the same throughout the study.
Nebulizing Equipment:	Pari LC-Jet Plus Nebulizer (with face mask or mouthpiece) and Pari Master compressor.

8.1.3.3 Prior and Concomitant Treatments

[60:24-5]

The following medications were not allowed prior to (with time restrictions indicated in parentheses) and during the study:

- Long-term use of systemic steroids (within 12 weeks of Visit 1).
- Intermittent use of systemic steroids (within 30 days prior to Visit 1).

- Inhaled glucocorticosteroids (within 8 hours prior to Visit 1). [61:6]
- Long-acting inhaled β_2-agonists (within seven days of Visit 1).
- Astemizole (within 90 days of Visit 1).
- Investigational drugs (within 30 days of Visit 1).
- Ipratropium bromide (within 48 hours of Visit 1).
- Combination preparations of expectorants and/or sedatives with bronchodilators, and over-the-counter asthma medications (within 24 hours of Visit 1).
- Hydrocortisone creams greater than 1%, except with the agreement from the Astra medical monitor.

Patients on immunotherapy must have been on a constant dose for at least two months prior to Visit 1, and remain on a constant regimen (dose and frequency) during the course of the study.

Patients on nasal steroids other than beclomethasone dipropionate (BDP) must have been switched to BDP at Visit 1, and the dose level should have remained constant throughout the study.

During the baseline phase, the patient's daily chronic asthma medications (with the exception of the excluded medications) were withdrawn, reduced, or kept constant per the judgment of the investigator. Breakthrough medication was to be continued.

During the treatment phase of the study, all asthma medications, with the exception of breakthrough medication were to be stopped prior to randomization at Visit 2.

Other medications not intended for asthma and considered necessary for the patient's welfare were permitted at the discretion of the investigator.

8.1.3.4 Efficacy Measurements and Variables

[60:25-8]
See Table 8.1.2 for the study procedures.

8.1.3.4.1 Procedures at the Clinic

- Spirometry testing was performed at all visits in patients capable of performing this procedure. All spirometric measurements were performed while the patient was standing and at approximately the same time of day, between 07:00 and 09:30 hours after at least 30 minutes rest.

The following drug washout periods were to be observed prior to spirometry testing:

- Inhaled glucocorticosteroids (Visits 1 and 2 only): 8 hours.
- Long-acting oral bronchodilators: 24 hours.
- Short-acting oral bronchodilators: 12 hours.
- Inhaled bronchodilators: 8 hours.
- Cromolyn sodium, nedocromil sodium: 8 hours.

- Antihistamines: 8 hours.
- Study Drug: 8 hours.

The following foods were restricted for at least eight hours prior PFTs: coffee, tea, chocolate, cola or other caffeine-containing beverages and/or foods; cold beverages and/or foods. Strenuous activity and strenuous physical exercise were not allowed within eight hours prior to PFTs or during clinic visits.

The FEV_1 (L), FVC (L) and corresponding $FEF_{25-75\%}$ (L/sec), were measured three times. The highest individual FEV_1 value, and the highest individual FVC with its corresponding $FEF_{25-75\%}$ were recorded on the CRF. The patient was to have demonstrated a baseline $FEV_1 \geq 50\%$ of Polgar's predicted at Visit 1 or 2, as determined by a computerized spirometer, or as calculated by the following formula, where Ht equals height in centimeters:

$$\text{Predicted Normal } FEV_1 = (2.1 \times 10^{-6})(Ht^{2.8})$$

- Reversibility testing was performed (Visits 1 or 2 in patients capable of performing the procedure) following the initial spirometry test. FEV_1 (L) was determined three times. The highest FEV_1 value was recorded in the CRF. The patient was required to have demonstrated a reversibility of bronchoconstriction $\geq 15\%$ at 15 ± 5 minutes after administration of a standard dose of inhaled bronchodilator. Reversibility was calculated using the following formula:

$$\frac{[FEV_{1\,AFTER}] - [FEV_{1\,BEFORE}]}{[FEV_{1\,BEFORE}]} \times [100]$$

- The patient's breakthrough medication (i.e., bronchodilator) was defined by the investigator on an individual patient basis (Visit 1).
- If the patient was capable of using a PEF meter, they were issued a [redacted] peak flow meter, and instructed on its proper use and care (Visit 1).
- The patient and/or legal guardian were issued daily diaries and were instructed on the proper way to measure and document morning and evening PEF (if applicable), daytime and nighttime asthma symptoms, daytime and nighttime use of breakthrough medication. Patients were instructed to bring their diaries with them to all subsequent clinic visits, at which time they were reviewed by the investigator's staff.

8.1.3.4.2 Assessments at Home

- Daytime and nighttime asthma symptom scores: Asthma symptom scores were assessed and recorded. Daytime was defined as the time period between the morning PEF assessment and the evening PEF assessment. Nighttime was defined as the time period between the evening PEF assessment and the morning and PEF assessment. Measurements were obtained every day during the baseline and treatment phases.

DAYTIME ASTHMA OVERALL SEVERITY SCORE:

0 = None; no symptoms of asthma.
1 = Mild symptoms; awareness of asthma symptoms and/or signs that are easily tolerated.
2 = Moderate symptoms; asthma symptoms and/or signs with some discomfort, causing some interference of daily activities.
3 = Severe symptoms; incapacitating asthma symptoms and/or signs, with inability to perform daily activities.

NIGHTTIME ASTHMA OVERALL SEVERITY SCORE:

0 = None; no symptoms of asthma.
1 = Mild symptoms; awareness of asthma symptoms and/or signs that are easily tolerated.
2 = Moderate symptoms; asthma symptoms and/or signs with some discomfort, causing some interference of sleep.
3 = Severe symptoms; incapacitating asthma symptoms and/or signs, with inability to sleep.

- Morning and evening PEF (if applicable): The highest of three measurements in the mornings (upon wakening) and in the evenings (approximately 12 hours later) were recorded. Attempts were made to perform the maneuvers at least five hours after the use of breakthrough medication. Measurements were obtained every day during the study.
- Daytime and nighttime use of breakthrough medication: The daytime and nighttime use of breakthrough medication, including dates and doses, were recorded. Measurements were obtained every day during the two-week baseline and the 12-week treatment phases.

8.1.3.5 Safety Measurements and Variables

[60:25-8]

8.1.3.5.1 Procedures at the Clinic

- A medical history was obtained and documented in the CRF (Visit 1 only).
- A physical examination with vital signs was performed (comprehensive exams were performed at Visits 1 and 6, and brief exams at Visits 2-5). Body length/height was measured in the same manner at all visits; for infants, with a recumbent table, and for standing children with a stadiometer.
- The patient/legal guardian was questioned regarding adverse events.
- Oropharyngeal and/or nasal cultures were obtained to determine the presence of fungi.
- Approximately one-half of the study sites obtained blood samples at Visits 1 and 6 to determine basal and post-ACTH stimulated plasma cortisol levels. Following the blood sample obtained between 06:00 and 08:30 hours, synthetic ACTH [redacted] was administered intravenously. If the patient was an infant, the synthetic ACTH could have been administered intramuscularly. A blood sample was obtained 60 minutes after the ACTH injection for determination of post-ACTH stimulation plasma cortisol levels.

- Clinical chemistry and hematology tests were performed at Visits 1 and 6 for safety assessments. The following laboratory variables were measured: hemoglobin, hematocrit, white blood cell count, differential white blood cell count, platelet count; serum BUN, sodium, creatinine, calcium, AST (SGOT), chloride, ALT (SGPT), potassium, total protein, total bilirubin, albumin, alkaline phosphate; urine glucose and protein.

The results of all the laboratory tests were assessed for clinical significance by the investigator. Any laboratory test results at Visit 1 that were outside the normal range were to be repeated before Visit 2 unless discussed with the Astra USA, Inc., medical monitor or designee. If the result on a repeat-test was again outside the normal range, the patient was not to be included in the study, or the investigator must have indicated in the CRF that (s)he believed the value was not clinically significant, and provided an explanation for the abnormal value.

All clinically significant worsenings from baseline in laboratory findings occurring after the first dose of study drug were recorded in the Adverse Event pages of the CRF, and the patient's values reviewed with the Astra USA, Inc., medical monitor before a decision was reached to allow the patient to remain in the study. Any tests at the final visit showing clinically significant worsenings from baseline values were repeated at a follow-up visit. Worsenings which persisted were to be followed after consultation with the Astra USA, Inc., medical monitor.

All clinically significant changes from baseline values, as judged by the investigator, were considered adverse events.

8.1.3.6 Adverse Events (AEs)

8.1.3.6.1 Adverse Event Definition

An AE was defined as any unintended, unfavorable clinical sign, symptom, medical complaint or clinically relevant change in laboratory test value, whether or not considered to be drug related. The definition could include reasons for changes in concomitant medication, any deterioration in concurrent illness or the development of clinically relevant changes in laboratory variables, ECG, X-ray or other clinical tests. It could also include reasons for referral to a consultant or admission to hospital (e.g., an accident, or an operation not planned previously).

Signs and/or symptoms of asthma (breathlessness, chest tightness, wheezing, cough with or without sputum) were not considered to be AEs in this study unless:

- there was a reasonable possibility that the signs and/or symptoms may have been actively caused by the study drug, or
- the signs and/or symptoms were serious according to study definitions, or
- the signs and/or symptoms were not consistent with the natural history of the subject's disease, as judged by the investigator.

8.1.3.6.2 Serious Adverse Event (SAE) Definition

An SAE was defined as one which suggested a significant hazard or disability to the patient. This included but was not limited to an AE which resulted in:

- death, or
- permanent or severe disability, or
- in-patient hospitalization or prolongation of existing in-patient hospitalization (Hospitalization which was planned before the study, and outpatient treatment in an emergency room were not in themselves considered SAEs. However, a change in the patient's condition resulting in earlier hospitalization was considered a SAE.), or was
- life threatening (Life threatening means that the patient was at immediate risk of death from the AE as it occurred. It does not mean that had the AE occurred in a more severe form it might have caused death.), or was
- a congenital anomaly, or
- cancer.

An AE fulfilling one of the criteria above was considered serious *even* if it was the result of a drug overdose, interaction or drug abuse.

A distinction was drawn between serious and severe AEs. A severe AE was defined as a major event of its type. A severe AE did not necessarily need to be considered serious. For example, nausea persisting for several hours may be considered severe nausea but need not be judged as a SAE. On the other hand, a stroke resulting in only a limited degree of disability may be considered a mild stroke but would be considered a SAE.

8.1.3.6.3 *Procedures for AE Reporting*

Assessing and reporting clinical symptoms: AEs were assessed by means of a standard question put to the patient and/or legal guardian upon arrival at the clinic. AEs reported by the patient and/or legal guardian, and the patient's and/or legal guardian's response to the standard question were recorded on the Adverse Event Form with information about seriousness, date of onset, duration, maximum intensity, action taken and outcome. The patient/legal guardian was asked to assess the intensity of the reported AE according to the following scale:

1 = **mild**; aware of symptom which is easily tolerated.
2 = **moderate**; discomfort enough to cause interference with daily life/usual activities.
3 = **severe**; incapacitating, with inability to attend day care/school or to take part in normal activities.

Any additional symptoms and/or temporary concomitant medications (together with reasons for its use) recorded by the patients in the diary cards and that were considered AEs were recorded on the Adverse Event Form in the CRF (unless they had been recorded on the current medical diagnosis form).