Table 5.1.5. Mean changes from baseline in efficacy variables.[1]

Mean Change from Baseline (Week 0-52)	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Asthma Symptom Score:		
Nighttime	-0.02	-0.02
95% CI	-0.27, 0.23	-0.19, 0.15
Daytime	-0.04	-0.03
95% CI	-0.30, 0.21	-0.21, 0.14
Use of Breakthrough Medication:		
Days	0.2	-1.1
95% CI	-2.0, 2.4	-2.7, 0.4
Nebulizations (of Nebulizer)/day	-0.37	-0.02
95% CI	-1.1, 0.3	-0.3, 0.3
Puffs (of pMDI)/day	-0.31	-0.24
95% CI	-0.4, 1.0	-0.8, 0.3
PEF (L/min):		
Morning	12.9	7.1
95% CI	-14.5, 40.3	-11.7, 25.8
Evening	13.5	8.9
95% CI	-14.4, 41.4	-10.3, 28.0
Spirometry[2]:		
FEV_1 (L/min)	0.15	0.10
95% CI	0.00, 0.31	-0.01, 0.21
FVC (L/min)	0.19	0.10
95% CI	-0.01, 0.38	-0.04, 0.23
$FEF_{25-75\%}$	0.14	0.06
95% CI	-0.09, 0.37	-0.10, 0.22
Proportion of Patients Discontinued (%)	13	13
Prednisone Use:		
Number (%) of Patients that Used Oral Prednisone During the Study:		
No	11 (37%)	27 (44%)
Yes	19 (63%)	34 (56%)
Average Total Daily Amount Used (mg):		
Mean±SD	1.40±2.71	0.65±0.93

[1] Data sources: Tables 5.1.4.1B, 5.1.4.4.1-4.

5.2 Study 04-3100B: A 52-Week Open-Label Safety and Efficacy Study of Budesonide (Pulmicort) Nebulizing Suspension Compared to Conventional Asthma Therapy in Children with Asthma Aged Eight Years and Younger.

5.2.1 Objectives

[IND 44,535; 6/22/1998; 8:15-6]

The primary objective of this multicenter, randomized, open-label, active-controlled, parallel-group study was to assess the long-term safety of the lowest individual maintenance dose of budesonide nebulizing suspension when administered for a period of up to 52 weeks, as compared to conventional asthma therapy (including inhaled GCS, β_2-agonists, methylxanthines and non-steroidal anti-inflammatories, per the judgment of the investigator). The study was preceded by a 12-week, double-blind, placebo-controlled treatment phase (Study 04-3100) that assessed the efficacy and safety of budesonide nebulizing suspension (0.25 mg QD, 0.25 mg BID, 0.5 mg BID and 1.0 mg QD) compared to placebo in 481 children aged 6 months to 8 years with persistent asthma not well-controlled on chronic asthma therapies.

5.2.1.1 Safety Variables

- Reported adverse events (AEs).
- Effects on HPA-axis function as assessed by pre- and post-ACTH-stimulation in a subset of patients.
- Changes in physical examinations, vital signs, and clinical laboratory tests (including oropharyngeal cultures).
- Changes in body length/height (stadiometry).
- Changes in skeletal age.

5.2.1.2 Efficacy Variables

- Mean changes from baseline in nighttime and daytime asthma symptom scores over the 52-week treatment phase.
- Patient outcome, including the proportion of patients who discontinued from the study for any reason and the proportion of patients who discontinued due to worsening asthma.
- The proportion of patients who took oral prednisone and the average daily amount of prednisone used for asthma deteriorations.
- The number of days breakthrough medication (short-term inhaled bronchodilator) was used.
- Spirometry variables (FEV_1, $FEF_{25-75\%}$ and FVC) performed at clinic.
- PEF measured daily in the morning and evening.
- Health status measurements, including the Modified Functional Status II (R) Scale Child Health Status Scale and the RAND General Health Index.
- Asthma-related health care utilization and indirect health care costs.

Reviewer's Comments: It is difficult to assess subjective efficacy endpoints in an open-label study without introducing bias.

5.2.2 Design

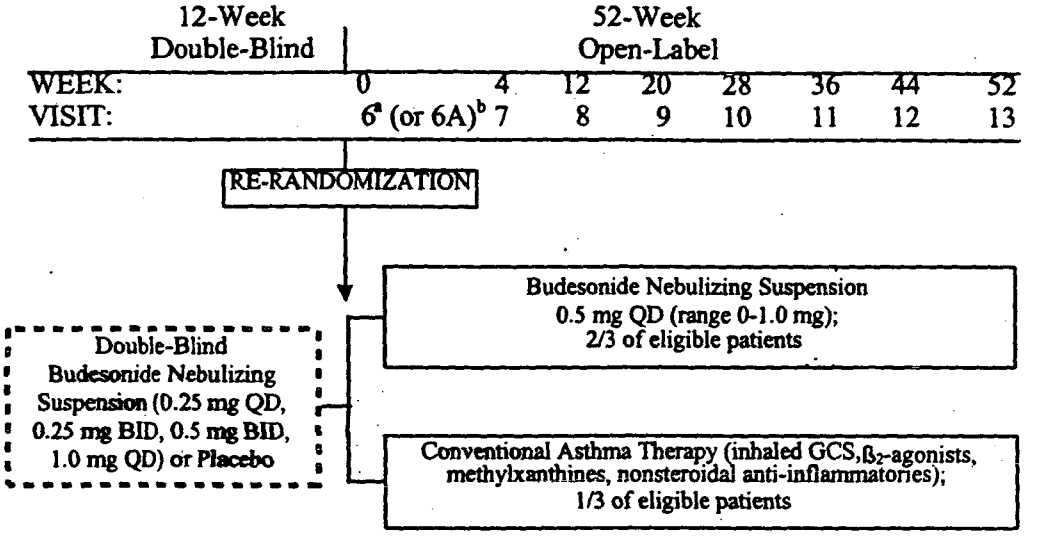
[IND 44,535; 6/22/1998; 8:16-9]

This was a multicenter, randomized, open-label, active-controlled, parallel-group study that was implemented as Amendment #1 to Study 04-3100. The original design of Study 04-3100 did not include an open-label treatment phase. Amendment #1 added the open-label extension to the study. A total of 307 patients were randomized at 29 centers located throughout the USA. Due to Amendment #1, these patients can be divided to 2 groups: (A) 56.7% of patients entered the open-label phase immediately after they had successfully completed the double-blind phase (Study 04-3100) or had discontinued due to worsening of asthma requiring oral corticosteroids. There was no washout period between the double-blind and the open-label treatment phases. (B) 43.3% of patients (43.1% of patients in the budesonide group; 43.7% of patients in the conventional asthma therapy group) entered the open-label phase after they had already completed the double-blind phase or had discontinued due to worsening of asthma requiring oral corticosteroids for various periods of time, and thus had a time lapse between the end of the double-blind phase and the beginning of the open-label phase, during which they were treated with conventional asthma medications (including inhaled corticosteroids) per the judgment of their physicians.

Two-thirds of the eligible patients were randomized to budesonide nebulizing suspension. These patients started the open-label phase with 0.5 mg budesonide QD in the morning with attempts to reduce the dose to 0.25 mg QD in AM, followed by 0.25 mg QOD in AM, followed by no budesonide treatment, as judged by the investigator. During asthma exacerbations, the patients were to be stabilized by increasing the dose of the breakthrough medications and/or by increasing the dose of budesonide nebulizing suspension (to a maximum dose of 1.0 mg QD in AM), followed by intermittent courses of oral prednisone as needed.

One-third of the eligible patients were randomized to conventional asthma therapy. These patients were treated with inhaled glucocorticosteroids, β_2-agonists, methylxanthines, and/or nonsteroidal anti-inflammatory agents (e.g., cromolyn sodium), as judged by the investigator. During asthma exacerbations, the patients were to be stabilized by combining the therapeutic agents mentioned above, followed by intermittent courses of oral prednisone as needed.

Figure 5.2.2. Open-Label Study Design. [IND 44,535; 6/22/1998; 8:17]



[a] Re-randomization into open-label for patients who completed or discontinued the double-blind phase AFTER implementation of Amendment #1; baseline for open-label.

[b] Re-randomization into open-label for patients who had already completed or discontinued the double-blind phase BEFORE implementation of Amendment #1; new baseline for open-label.

Table 5.2.2. Schedule of Open-Label Visits and Procedures. [IND 44,535; 6/22/1998; 8:18]

OPEN-LABEL WEEK NUMBER:	0	0	4	12	20	28	36	44	52
VISIT NUMBER:	6[a]	6A[b]	7	8	9	10	11	12	13[c]
CLINICAL ASSESSMENTS:									
Open-Label Informed Consent Form	X	X							
Updated Medical History		X							
Comprehensive Physical Examination with Vital Signs	X	X[d]							X
Brief Physical Examination with Vital Signs		X[d]	X	X	X	X	X	X	
Left Hand-Wrist X-Ray	X	X[e]							X
Body Length/Height (Stadiometry), Weight	X	X	X	X	X	X	X	X	X
Pulmonary Function Test[f]	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS:									
Hematology, Blood Chemistry	X	X[g]		X		X			X
Urinalysis	X	X[g]		X		X			X
Basal & Post-ACTH Cortisol Levels[h]	X	X[g]							X
Oropharyngeal and/or Nasal Fungal Cultures[i]	X	X[g]							X
OTHER:									
Quality of Life Questionnaire	X	X				X			X
Review Adverse Events	X	X	X	X	X	X	X	X	X
Review Daily Diaries (asthma symptoms, use of breakthrough medications, PEF)	X		X	X	X	X	X	X	X
Review Health Outcome Diaries	X		X	X	X	X	X	X	X
Return Study Drug/Assess Compliance	X		X	X	X	X	X	X	X
Practice and/or Review Inhalation Technique, PEF Technique, Use/Care of Equipment	X	X	X	X	X	X	X	X	
Dispense Study Drug/ Nebulizing Equipment	X	X	X	X	X	X	X	X	
Dispense New Diaries	X	X	X	X	X	X	X	X	

[a] Re-randomization into open-label for patients who prospectively completed or discontinued the double-blind phase AFTER implementation of Amendment #1; baseline for open-label.

[b] Re-randomization into open-label for patients who had already completed or discontinued the double-blind phase BEFORE implementation of Amendment #1; new baseline for open-label.

[c] Final visit of open-label.

[d] Patients with a ≤14 day window between double-blind and Visit 6A needed only a brief physical examination with vital signs.

[e] If not done within the previous 30 days.

[f] $FEV_{1.0}$, FVC, $FEF_{25-75\%}$, for patients that could perform PFT.

[g] Patients with a ≤ 30-day window between double-blind and Visit 6A did not need to perform laboratory assessments at this visit.

[h] Selected clinical sites only.

[i] Repeated as judged necessary by the investigator.

5.2.3 Protocol

5.2.3.1 Selection of Study Population

[IND 44,535; 6/22/1998; 8:19]

5.2.3.1.1 Inclusion Criteria

3. The patient completed the 12-week double-blind phase of the study (Study 04-3100), or was discontinued from the double-blind phase because of the need for oral corticosteroids for worsening airways disease.
4. The patient's health would not be compromised by participating in the open-label phase, per the judgment of the investigator.

5.2.3.1.2 Exclusion Criteria

There were no additional exclusion criteria for this phase of the study.

5.2.3.2 Study Drugs

[IND 44,535; 6/22/1998; 8:20-1]

Same as those in Study 04-3100 except different batches (Original review: Section 8.1.3.2).

5.2.3.3 Concomitant Treatments

[IND 44,535; 6/22/1998; 8:23]

The following medications were not allowed:

- Long-acting inhaled β_2-agonists
- Astemizole
- Over-the-counter asthma medications

The following were allowed with the appropriate restrictions (e.g., prior to PFT):

- Asthma medication: Patients randomized to conventional asthma therapy could have been treated with inhaled GCS, short-acting β_2-agonists, methylxanthines, and/or inhaled nonsteroidal anti-inflammatory agents (e.g., cromolyn sodium), as judged necessary by the investigator.
- Oral corticosteroids: Intermittent courses of oral prednisone were allowed for the control of asthma exacerbations, as judged by the investigator.

Other medications considered necessary for the patient's welfare were permitted at the discretion of the investigator.

5.2.3.4 Efficacy Measurements and Variables

[IND 44,535; 6/22/1998; 8:24-29]

Apart from using a slightly different schedule, the procedures of efficacy measurements in this study were the same as those in Study 04-3069B (Original review: Sections 8.4.3.4).

5.2.3.5 Safety Measurements and Variables

[IND 44,535; 6/22/1998; 8:24-29]

Apart from using a slightly different schedule, the procedures of safety measurements in this study were the same as those in Study 04-3069B (Original review: Section 8.4.3.5) except the following modifications and/or addition:

- Left hand-wrist x-rays were taken at Visits 6 (or 6A) and Visit 13

5.2.3.6 Adverse Events (AEs)

[IND 44,535; 6/22/1998; 8:29-32]
Same as those in Study 04-3100 (Original review: Section 8.1.3.6).

5.2.3.7 Treatment and Measurement Discontinuation

[IND 44,535; 6/22/1998; 8:19-20]
Same as those in Study 04-3100 (Original review: Section 8.1.3.7).

5.2.3.8 Statistical Analysis

[IND 44,535; 6/22/1998; 8:33-39]
Same as those in Study 04-3069B (Original review: Sections 8.4.3.8) except the analysis of changes in skeletal age, which was the same as that in Study 04-3072B (Section 5.1.3.8.)

5.2.4 Results

5.2.4.1 Patient Disposition

[IND 44,535; 6/22/1998; 8:38-40]
The patterns of the distribution of the patients by their previous double-blind treatment assignment were similar in both treatment groups.

Table 5.2.4.1A. Distribution of Randomized Patients by Their Previous Double-Blind Treatment Assignment. [IND 44,535; 6/22/1998; 8:75]

Previous Double-Blind Treatment	Open-Label Treatment		Total
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension	
	(n=103)	(n=204)	(n=307)
Placebo:	19 (18%)	39 (19%)	58 (19%)
Budesonide Nebulizing Suspension:			
0.25 mg QD	22 (21%)	44 (22%)	66 (21%)
0.25 mg BID	20 (19%)	42 (21%)	62 (20%)
0.5 mg BID	23 (22%)	45 (22%)	68 (22%)
1.0 mg QD	19 (18%)	34 (17%)	53 (17%)

The proportion of patients who discontinued from the study in the conventional therapy group was significantly greater than that for the budesonide group (29% vs. 13%, respectively; p=0.001). This was attributed to the fact that non-compliance with the study

procedures, withdrawal of consent, and loss of follow-up was found more often in the conventional therapy group (27%) compared to the budesonide group (11%). Due to the same reason, the Kaplan-Meier estimate of the time to discontinuation from the study therapy showed that the patients on budesonide remained longer on study therapy compared to those on conventional therapy (p=0.003; log rank test).

Table 5.2.4.1B. Summary of Patient Deposition. [IND 44,535; 6/22/1998; 8:78-81]

Patient Disposition	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Randomized	103	204
Completed Open-Label Treatment	73 (71%)	177 (87%)
Total No. Patients Discontinued:	30 (29%)***	27 (13%)
Worsening Asthma[1]	1 (<1%)	2 (<1%)
Adverse Event	0 (0%)	1 (<1%)
Use of Medication Excluded by Protocol[2]	1 (<1%)	1 (<1%)
Non-Compliance w/Study Procedures	7 (7%)	7 (3%)
Withdrew Consent	15 (15%)	11 (5%)
Lost to Follow-up	6 (6%)	5 (2%)
Evaluated for Efficacy Analyses	103	204
Evaluated for Safety	103	204

[1] Includes patients who were discontinued due to lack of therapeutic effect or disease deterioration, and patients who received drugs for asthma not permitted by the protocol.
[2] Non-permitted medications for indications other than asthma.
*** p=0.001, conventional asthma therapy versus budesonide nebulizing suspension.

Reviewer's Comments: The proportion of patients who discontinued from the study is not a meaningful efficacy endpoint in this study since most discontinuations were due to causes other than worsening asthma, adverse events, or use of non-permitted medications.

5.2.4.2 Demographic and Other Open-Label Baseline Characteristics

[IND 44,535; 6/22/1998; 8:43-44, 84-5]

Prior to the open-label phase, 81% of the patients had completed the 12-week double-blind phase and 19% (29.1% of conventional therapy patients and 13.2% of budesonide patients) had discontinued the study due to worsening of asthma requiring the use of oral glucocorticosteroids.

Among basic demographic characteristics, the mean age, weight, and height as well as the proportion of Black and Hispanic patients were slightly higher in the conventional therapy group compared to the budesonide group.

Table 5.2.4.2. Demographic and Baseline Characteristics.

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
n	103	204
Gender:		
Male	67 (65.0%)	127 (62.3%)
Female	36 (35.0%)	77 (37.7%)
Age (months):		
Mean ± SD	58.7±28.9	56.7±25.2
Range	12-109	12-113
Race:		
Caucasian	76 (73.8%)	169 (82.8%)
Black	19 (18.4%)	25 (12.3%)
Hispanic	6 (5.8%)	7 (3.4%)
Oriental	0 (0%)	1 (0.5%)
Other	2 (1.9%)	2 (1.0%)
Weight; Mean ± SD:		
Pounds	46.4±19.7	44.4±18.4
Kilograms	21.0±8.9	20.1±8.3
Height (cm); Mean ± SD	108.2±17.9	107.1±15.9
Double-Blind Phase:		
Completion	73 (70.9%)	177 (86.8%)
Discontinuation	30 (29.1%)	27 (13.2%)

Data source: [IND 44,535; 6/22/1998; 8:84-5]

5.2.4.2.1 *Baseline Asthma Symptom Scores, Pulmonary Function Test Data, and Breakthrough Medication Use*

[IND 44,535; 6/22/1998; 8:44-5]

Compared to the budesonide group, the conventional asthma therapy group had higher nighttime asthma symptom scores, daytime asthma symptom scores, and number of days use of breakthrough medication at baseline (last 14 days of double-blind therapy).

Reviewer's Comments: More conventional therapy patients (29.1%) than budesonide patients (13.2%) had discontinued the double-blind phase due to worsening of asthma. (Section 5.2.4.2). In addition, patients in the conventional therapy group had poorer control of asthma at the baseline, (i.e., higher asthma symptom scores, and higher number of days use of breakthrough medication). These observations confound the interpretation of comparative growth data.

Table 5.2.4.2.1. Baseline Lung Function, Asthma Symptom Scores, and Number of Days Use of Breakthrough Medication. [IND 44,535; 6/22/1998; 8:86-8].

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	**Budesonide Nebulizing Suspension**
Nighttime Asthma Symptom Scores:		
Mean±SD	0.85±0.65 (n=90)	0.62±0.60 (n=198)
Daytime Asthma Symptom Scores:		
Mean±SD	0.95±0.67 (n=90)	0.65±0.59 (n=194)
Number of Days Use of Breakthrough Medication:		
Mean±SD	5.9±7.2 (n=90)	3.8±6.0 (n=198)
PFT Able:		
No	68 (66.0%)	142 (69.6%)
Yes	35 (34.0%)	62 (30.4%)
FEV_1 (L/sec):	1.36±0.24	1.27±0.28
% Predicted FEV_1:	84.07±13.80 (n=35)	84.41±15.34 (n=60)
Morning PEF (L/min):	186.1±37.5 (n=31)	183.6±57.1 (n=57)
Evening PEF (L/min):	189.7±35.7 (n=31)	179.8±60.8 (n=54)

5.2.4.2.2 *Baseline (Visit 6 of Visit 6A) Physical Examination*

[IND 44,535; 6/22/1998; 8:46, 89-91]

In general, the treatment groups were similar with respect to general physical condition at baseline. Forty-five percent of patients had abnormal findings in the nasal/other examination category; 44% in the conventional therapy group and 46% in the budesonide group.

5.2.4.2.3 *Medications Taken During Open-Label*

[IND 44,535; 6/22/1998; 8:47-8]

5.2.4.2.3.1 Asthma Medications

Study Medications; General: The mean number of days on study therapy for the patients on budesonide (343 days) was higher than that for those on conventional therapy (308 days).

Table 5.2.4.2.3.1. Duration of Exposure (Days) to Open-Label Treatment. [IND 44,535; 6/22/1998; 8:140]

Duration of Treatment (Days)	Budesonide Nebulizing Suspension[1]	Conventional Asthma Therapy
N	198	97
Mean±SD	343±83	308±116
Median	365	365
Minimum	1	1
Maximum	414	400

[1] 6 patients in each treatment group had no dates from which to calculate duration of therapy.

Study Medications; Budesonide Nebulizing Suspension:
The mean total daily dose of budesonide nebulizing suspension was between 0.50 mg and 0.54 mg over the course of the study. One-hundred and thirty-seven (67.2%) patients were titrated down and up; 28 (13.7%) were titrated down and stayed down; 11 (5.4%) were titrated up and stayed up; 28 (13.7%) remained on the initial 0.5 mg QD dose. [IND 44,535; 6/22/1998; 8:93]

Study Medications; Conventional Asthma Therapy Medications:
The conventional asthma therapies used were cromolyn sodium (58%), albuterol (39%), beclomethasone (25%), triamcinolone (13%), flunisolide (8%), theophylline (5%), ipratropium (<1%) and terbutaline (<1%). [IND 44,535; 6/22/1998; 8:94]

Added Asthma Medications (Concomitant asthma medications): Among asthma medications added during the open-label phase (i.e., not budesonide or conventional asthma therapy assigned by the investigator) not including prednisone, albuterol was the medication used by the greatest number of patients (87%), followed by cromolyn sodium (22%), beclomethasone (3%), theophylline (3%), and triamcinolone (2%). More patients (97%) in the budesonide group used albuterol as a concomitant asthma medication compared to the conventional therapy group (68%). Albuterol could have been added on as maintenance therapy in addition to being used already as breakthrough medication, and that the distinction between the two uses was not always clear. [IND 44,535; 6/22/1998; 8:95]

For patients with a time lapse between the double-blind phase and the open-label phase, beclomethasone was the steroid asthma medication used by the greatest number of patients (18%) between Visits 6 and 6A. The use of steroid asthma medications in the two treatment groups were the same during this period. [IND 44,535; 6/22/1998; 8:106]

5.2.4.2.3.2 Non-Asthma Medications

Concomitant non-asthma medications:
The use of concomitant non-asthma medications was generally similar between treatment groups. Drug classes mentioned most frequently were systemic antibacterials (78%), other dermatologic preparations (67%), nasal preparations (60%), analgesics (41%), systemic antihistamines (34%), and cough and cold preparations (31%). [IND 44,535; 6/22/1998; 8:96-105]

Reviewer's Comments: Psycholeptics were used more frequently in the budesonide group (12%) than in the conventional therapy group (2%). [IND 44,535; 6/22/1998; 8:96-105] *This might be treatment related since psychiatric disorders were also reported slightly more frequently in the budesonide group.* (Section 5.2.4.5.2.2) *A similar finding was also observed in Study 3072B* (Section 5.1.4.2.3.2), *but not in Study 3069 B* [110:90].

5.2.4.3 Measurements of Treatment Compliance

[IND 44,535; 6/22/1998; 8:49; 10:6.1]

The compliance with respect to administration of study drug during the 52-week treatment period was 84-93% in the budesonide group and not assessed in the conventional therapy group.

5.2.4.4 Efficacy Analysis

[IND 44,535; 6/22/1998; 8:49-52]

5.2.4.4.1 Asthma Symptoms and Prednisone Use

The mean changes of nighttime and daytime asthma symptom scores from baseline (last 14 days of double-blind) to the last observation were similar between the two treatment groups.

A slightly higher percent of patients from the conventional therapy group (54%) required the use of oral prednisone compared to the budesonide group (51%). The mean and median total daily doses of oral prednisone used by patients in the conventional asthma therapy group were also slightly higher compared to the budesonide group.

Table 5.2.4.4.1. Mean Changes From Baseline (Last 14 Days Of Double-Blind) to the Last Observation in Asthma Symptom Scores (Scale Of 0-3) and Oral Prednisone Use.

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Asthma Symptom Score:[1]		
Mean Change from Baseline		
Nighttime	-0.08	-0.10
95% CI	-0.19, 0.03	-0.19, -0.02
(n)	(90)	(198)
Daytime	-0.10	-0.09
95% CI	-0.22, 0.01	-0.18, -0.00
(n)	(90)	(194)
Prednisone Use:[2]		
Number (%) of Patients that Used Oral Prednisone During the Study:		
No	47 (46%)	99 (49%)
Yes	56 (54%)	105 (51%)
Average Total Daily Amount Used (mg):		
Mean±SD	0.63±0.97	0.58±1.38
Median	0.24	0.11
	(n=103)	(n=204)

[1] Data sources: [IND 44,535; 6/22/1998; 8:108-9]
[2] Data sources: [IND 44,535; 6/22/1998; 8:113-4]

Reviewer's Comments: Compared to the budesonide group, the proportion of patients that used oral prednisone and the mean and median of average total daily amount used were slightly higher in the conventional therapy group. This may confound the interpretation of comparative growth data, albeit to a small degree.

5.2.4.4.2 Breakthrough Medication Use

No consistent differences were observed in the mean changes from baseline (last 14 days of double-blind) to the last open-label observation in the number of days of breakthrough medication use and the number of nebulizations (nebulizer)/day and puffs (pMDI)/day of breakthrough medication. These results should be interpreted with caution since albuterol could have been used as maintenance therapy in addition to being used as breakthrough medication, and the distinction between the two uses was not always clear.

Table 5.2.4.4.2. Mean Changes from Baseline (Last 14 Days of Double-Blind) to the Last Observation in the Use of Breakthrough Medication. [IND 44,535; 6/22/1998; 8:110-2]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Use of Breakthrough Medication:		
Mean Change from Baseline		
Days	-1.0	-0.5
95% CI	-1.9, -0.1	-1.2, 0.2
(n)	(90)	(198)
Nebulizations (of Nebulizer)/day	0.07	-0.02
95% CI	-0.1, 0.3	-0.2, 0.1
(n)	(53)	(138)
Puffs (of pMDI)/day	-0.25	-0.03
95% CI	-0.7, 0.2	-0.4, 0.3
(n)	(26)	(46)

5.2.4.4.3 *Morning and Evening PEFs*

Both treatment groups showed similar improvements, with the 95% CIs overlapping between the two treatment groups.

Table 5.2.4.4.3. Mean Changes from Baseline (Last 14 Days of Double-Blind) to the Last Observation in Morning and Evening PEFs. [IND 44,535; 6/22/1998; 8:118, 122]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
PEF (L/min):		
Mean Change from Baseline		
Morning	8.3	8.6
95% CI	-13.1, 29.9	-7.1, 24.4
(n)	(31)	(57)
Evening	8.5	12.0
95% CI	-13.1, 30.0	-3.9, 27.9
(n)	(31)	(54)

5.2.4.4.4 *FEV_1, FVC and corresponding $FEF_{25-75\%}$*

Improvement in FEV_1 and FVC was similar in both groups.

Table 5.2.4.4.4. Mean Changes From Baseline (Last Visit of Double-Blind) to the Last Observation in FEV_1, FVC and Corresponding $FEF_{25-75\%}$. [IND 44,535; 6/22/1998; 8:119-21]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Spirometry:		
Mean Change from Baseline		
FEV_1 (L/min)	0.07	0.06
95% CI	-0.05, 0.18	-0.03, 0.14
(n)	(32)	(57)
FVC (L/min)	0.13	0.08
95% CI	-0.03, 0.28	-0.03, 0.19
(n)	(32)	(57)
$FEF_{25-75\%}$	0.00	0.04
95% CI	-0.17, 0.17	-0.08, 0.17
(n)	(32)	(57)

5.2.4.4.5 *Modified Functional Health Status FS-II (R); Health Status FS-II (R) General and FS-II (R) Specific*

The increase in FS-II (R) General scores, reflecting the patient's functional status, was numerically higher in patients on budesonide than those on conventional therapy.

Reviewer's Comments: In an open-label study, the clinical significance of changes in FS-II (R) general scores is uncertain. Between the two treatment groups, the difference in changes in FS-II (R) general scores and the difference in asthma symptom scores, pulmonary function, or the use of breakthrough medication were not parallel.

Table 5.2.4.4.5. Mean Changes from Baseline (Last Double-Blind Observation) to the Last Observation in Modified Functional Health Status FS-II (R) General and Specific Scores. [IND 44,535; 6/22/1998; 8:115]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
FS-II Scores:		
Mean Change from Baseline		
General	2.0	2.9
95% CI	-1.0, 4.9	0.3, 5.4
(n)	(93)	(186)
Specific	2.4	3.8
95% CI	-0.4, 5.2	1.4, 6.2
(n)	(93)	(186)

5.2.4.4.6 *Child Health Status Questionnaire (RAND-ALL)*

The Child Health Status data showed that patients in both treatment groups improved health status during open-label phase. The increase in RAND-ALL scores in the budesonide group was numerically higher than that in the conventional therapy group.

Reviewer's Comments: The clinical significance of changes in RAND-ALL scores is uncertain. Between the two treatment groups, the difference in changes in RAND-ALL scores and the difference in asthma symptom scores, pulmonary function, or the use of breakthrough medication were not parallel.

Table 5.2.4.4.6. Mean Changes From Baseline (Last Double-Blind Observation) to the Last Observation in the RAND-ALL Child Health Status Score. [IND 44,535; 6/22/1998; 8:116]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Mean Change from Baseline		
RAND-ALL Score	4.5	7.1
95% CI	0.8, 8.2	4.6, 9.6
(n)	(83)	(202)

5.2.4.4.7 *Health Care Utilization*

In general, the health care utilization variables and indirect economic endpoints were not very different between the two treatment groups. The percent of patients with emergency room visits or asthma-related emergency room visits was slightly higher in the conventional therapy group compared to the budesonide group.

Table 5.2.4.4.7. Health Care Utilization During Open-Label Treatment, Weeks 0 to 52.

Variable	Treatment Group	Total N	Number (%) of Patients With Response
Days Absent from School[1]	Budesonide	184	166 (90%)
	Conventional	84	74 (88%)
Asthma Related Days Absent From School[1]	Budesonide	184	165 (90%)
	Conventional	84	74 (88%)
Days Routine Interrupted	Budesonide	199	170 (85%)
	Conventional	92	78 (85%)
Unscheduled Doctor Visits	Budesonide	199	170 (85%)
	Conventional	92	77 (84%)
Asthma Related Unscheduled Doctor Visits	Budesonide	199	171 (86%)
	Conventional	92	76 (83%)
Emergency Room Visits	Budesonide	199	82 (41%)
	Conventional	92	45 (49%)
Asthma Related Emergency Room Visits	Budesonide	199	85 (43%)
	Conventional	92	46 (50%)
Hospitalizations	Budesonide	199	43 (22%)
	Conventional	92	21 (23%)

[1] Only those children attending school/play school/daycare were included.
Data Source: [IND 44,535; 6/22/1998; 8:117]

5.2.4.5 Safety Analysis

[IND 44,535; 6/22/1998; 8:53-71]

5.2.4.5.1 Extent of Exposure

See Section 5.2.4.2.3.1.

5.2.4.5.2 Adverse Events

[IND 44,535; 6/22/1998; 8:54-62]

5.2.4.5.2.1 Brief Summary of Adverse Events

There were no deaths reported during the study. A total of 33 serious AEs (SAEs) in 28 patients (11 SAEs in 11 (11%) patients in the conventional therapy group; 22 SAEs in 17 (8%) patients in the budesonide group) were reported (Table 5.2.4.5.2.4). One patient was discontinued from the budesonide group due to unusual behavior.

The percentage of reported severe AEs in the budesonide group (23%) were slightly higher than that in the conventional therapy group (17%). After adjusting for the length of time in the study there were no statistically significant differences in the frequency of reported AEs.

5.2.4.5.2.2 Display of All Adverse Events

A total of 289 (94%) patients experienced adverse events. The most frequently reported AEs included respiratory infection (52%), sinusitis (37%), fever (28%), otitis media (24%), and pharyngitis (22%). After adjusting for the length of time in the study there were no statistically significant differences in the frequency of reported AEs between the two treatment groups (Table 5.2.4.5.2.2.B).

Table 5.2.4.5.2.2.A. Summary of Reported Adverse Events. [IND 44,535; 6/22/1998; 8:54, 142]

	Budesonide Nebulizing Suspension (n=204)	Conventional Asthma Therapy (n=103)
No. of Patients with ≥1 AE	196 (96%)	93 (90%)
No. of Patients with ≥1 Drug Related AE	23 (11%)	10 (10%)
No. of Patients with ≥1 SAE	17 (8%)	11 (11%)
No. of Patients with ≥1 severe AE	47 (23%)	17 (17%)
No. of Patients Who Discontinued from the Study Due to AEs	1 (<1%)	0 (0%)

Reviewer's Comments: 1. The AEs with a relative risk >2 (the budesonide group versus the conventional therapy group) included vomiting, urticaria, and earache. The significance of these observations was not clear. Interestingly, in Study 3072B the AEs with a relative risk >2 also included vomiting and earache. 2. Psychiatric disorders were reported more frequently in the budesonide group (unusual behavior, 1%; nervousness, 1%; aggressive reaction, 0.5%; euphoria, 0.5%; paroniria, 0.5%) than in the conventional therapy group (unusual behavior, 1%). [IND 44,535; 6/22/1998; 1:133] *A similar finding was also observed in Study 3072B (*[illegible]*ction 5.1.4.5.2.2), but not in Study 3069 B* [110:143-4].

Table 5.2.4.5.2.2B. Summary of Most Frequently Reported AEs (≥3% of Patients in Any Treatment Group) that Began During Open-Label Treatment with Relative Risks (From Proportional Hazards Model) and 95% Confidence Interval, and Adjusted for Length of Time (Per 12 Patient-Months) in the Study.

Body System/AE [1]	Incidence of AEs Beginning in Open-Label					Frequency per 12 Pt-Months	
	Conv. Asthma Therapy (n=103)	Budesonide Nebulizing Suspension (n=204)	Total (n=307)	Relative Risk	95% Confidence Interval	Conv. Asthma Therapy	Budesonide Nebulizing Suspension
Respiratory System Disorders							
Respiratory Infection	48 (47%)	111 (54%)	159 (52%)	0.924	(0.66, 1.30)	0.6	0.6
Sinusitis	32 (31%)	81 (40%)	113 (37%)	1.111	(0.74, 1.67)	0.4	0.4
Pharyngitis	22 (21%)	46 (23%)	68 (22%)	0.858	(0.52, 1.43)	0.3	0.2
Rhinitis	10 (10%)	38 (19%)	48 (16%)	1.753	(0.87, 3.52)	0.1	0.2
Bronchitis	8 (8%)	27 (13%)	35 (11%)	1.472	(0.67, 3.24)	0.1	0.1
Coughing	6 (6%)	19 (9%)	25 (8%)	1.425	(0.57, 3.57)	0.1	0.1
Bronchospasm	8 (8%)	15 (7%)	23 (7%)	0.781	(0.33, 1.84)	0.1	0.1
Pneumonia	6 (6%)	15 (7%)	21 (7%)	1.095	(0.42, 2.82)	0.1	0.1
Stridor	4 (4%)	8 (4%)	12 (4%)	0.846	(0.25, 2.81)	0.1	0.0
Body as a Whole							
Fever	22 (21%)	64 (31%)	86 (28%)	1.373	(0.85, 2.23)	0.3	0.3
Accident and/or Injury	13 (13%)	31 (15%)	44 (14%)	1.032	(0.54, 1.97)	0.2	0.2
Flu-Like Disorder	4 (4%)	12 (6%)	16 (5%)	1.273	(0.41, 3.95)	0.1	0.1
Pain	4 (4%)	10 (5%)	14 (5%)	1.074	(0.34, 3.42)	0.1	0.1
Allergic Reaction	4 (4%)	2 (<1%)	6 (2%)	0.209	(0.04, 1.14)	0.1	0.0

Table G continued on next page.

Body System/AE [1]	Incidence of AEs Beginning in Open-Label					Frequency per 12 Pt-Months	
	Conv. Asthma Therapy (n=103)	Budesonide Nebulizing Suspension (n=204)	Total (n=307)	Relative Risk	95% Confidence Interval	Conv. Asthma Therapy	Budesonide Nebulizing Suspension
Resistance Mechanism Disorders							
Otitis Media	23 (22%)	50 (25%)	73 (24%)	0.951	(0.58, 1.56)	0.3	0.3
Infection Viral	14 (14%)	19 (9%)	33 (11%)	0.572	(0.29, 1.14)	0.2	0.1
Moniliasis	3 (3%)	13 (6%)	16 (5%)	1.791	(0.51, 6.29)	0.0	0.1
Varicella	2 (2%)	9 (4%)	11 (4%)	1.749	(0.37, 8.24)	0.0	0.0
Infection	5 (5%)	7 (3%)	12 (4%)	0.604	(0.19, 1.90)	0.1	0.0
Gastrointestinal System Disorders							
Gastroenteritis	9 (9%)	19 (9%)	28 (9%)	0.887	(0.40, 1.96)	0.1	0.1
Vomiting	2 (2%)	16 (8%)	18 (6%)	3.544	(0.81, 15.4)	0.0	0.1
Abdominal Pain	4 (4%)	10 (5%)	14 (5%)	1.068	(0.33, 3.40)	0.1	0.1
Diarrhea	5 (5%)	8 (4%)	13 (4%)	0.673	(0.22, 2.06)	0.1	0.0
Nausea	3 (3%)	4 (2%)	7 (2%)	0.566	(0.13, 2.53)	0.0	0.0
Dyspepsia	3 (3%)	3 (1%)	6 (2%)	0.422	(0.09, 2.09)	0.0	0.0
Skin & Appendages Disorders							
Rash	5 (5%)	15 (7%)	20 (7%)	1.321	(0.48, 3.63)	0.1	0.1
Eczema	3 (3%)	11 (5%)	14 (5%)	1.608	(0.45, 5.77)	0.0	0.1
Urticaria	2 (2%)	11 (5%)	13 (4%)	2.413	(0.53, 10.8)	0.0	0.1
Rash Pustular	2 (2%)	6 (3%)	8 (3%)	1.284	(0.26, 6.36)	0.0	0.0
Central & Peripheral Nervous Sys. Disorder							
Headache	4 (4%)	16 (8%)	20 (7%)	1.759	(0.59, 5.26)	0.1	0.1

Table G continued on next page.

Body System/AE [1]	Incidence of AEs Beginning in Open-Label					Frequency per 12 Pt-Months	
	Conv. Asthma Therapy (n=103)	Budesonide Nebulizing Suspension (n=204)	Total (n=307)	Relative Risk	95% Confidence Interval	Conv. Asthma Therapy	Budesonide Nebulizing Suspension
Hearing & Vestibular Disorders							
Ear Infection NOS	11 (11%)	31 (15%)	42 (14%)	1.210	(0.61, 2.41)	0.1	0.2
Ear Ache	0 (0%)	7 (3%)	7 (2%)	$>10^6$	(0.0, .. 0)	0.0	0.0
Vision Disorders							
Conjunctivitis	7 (7%)	14 (7%)	21 (7%)	0.856	(0.35, 2.12)	0.1	0.1
Musculo-Skeletal System Disorders							
Fracture	4 (4%)	2 (<1%)	6 (2%)	0.210	(0.04, 1.15)	0.1	0.0
Urinary System Disorders							
Urinary Tract Infection	3 (3%)	5 (2%)	8 (3%)	0.692	(0.17, 2.90)	0.0	0.0

[1] Data source: [IND 44,535; 6/22/1998; 8:147-54]

5.2.4.5.2.3 Analysis of Adverse Events

The incidence of all AEs considered by the investigator to be possibly or probably related to treatment was very similar between the budesonide group (11%) and the conventional therapy group (10%). Moniliasis was reported in 10 (5%) patients on budesonide and in 4 (4%) on conventional therapy. Hyperkinesia was reported in 3 (1%) patients on budesonide and in 1 (<1%) on conventional therapy. The incidence of all other possibly or probably treatment-related AEs was low (<1%) and similar between the two treatment groups. [IND 44,535; 6/22/1998; 8:155-6]

5.2.4.5.2.4 Serious Adverse Events

There were no deaths reported during this study. A total of 33 SAEs in 28 patients were reported (11 events in 11 (11%) patients in the conventional therapy group; 22 events in 17 (8%) patients in the budesonide group).

Table 5.2.4.5.2.4. Summary of Serious Adverse Events.[1]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Budesonide Nebulizing Suspension:		
08-0449	Gastroenteritis/completely recovered.	Unlikely
10-0162	Pneumonia/completely recovered.	Unlikely
13-0349	Bronchospasm/completely recovered.	Unlikely
14-0219	Accident/Injury	Unlikely
14-0753	Bronchospasm/completely recovered.	Unlikely
	Bronchospasm/completely recovered.	Unlikely
17-0248	Lymphadenopathy/completely recovered.	Unlikely
17-0596	Accident/Injury	Unlikely
19-0726	Dehydration/completely recovered.	Unlikely
20-0481	Bronchospasm/completely recovered.	Unlikely
22-0391	Pneumonia Lobar/completely recovered.	Unlikely
22-0647	Urinary Tract Infection/completely recovered.	Unlikely
23-0510	Bronchospasm/completely recovered.	Unlikely
23-0511	Bronchospasm/completely recovered.	Unlikely
30-0401	Bronchospasm/completely recovered.	Unlikely
	Bronchospasm/completely recovered.	Unlikely
	Bronchospasm/completely recovered.	Unlikely
33-0567	Bronchospasm/completely recovered.	Unlikely
	Bronchospasm/completely recovered.	Unlikely
33-0569	Bronchospasm/completely recovered.	Unlikely
	Bronchospasm/completely recovered.	Unlikely
35-0601	Dehydration/completely recovered.	Unlikely
Conventional Asthma Therapy:		
02-0713	Dehydration/completely recovered.	Unlikely
14-0217	Bronchospasm/completely recovered.	Unlikely
14-0220	Pneumonia/completely recovered.	Unlikely
21-0491	Abdominal Pain[3]/completely recovered.	Unlikely
22-0643	Bronchospasm/completely recovered.	Unlikely
23-0812	Lymphadenopathy/completely recovered.	Unlikely
25-0255	Pneumonia/completely recovered.	Unlikely
27-0281	Bronchospasm/completely recovered.	Unlikely
28-0301	Convulsions/completely recovered.	Unlikely
31-0586	Bronchospasm/completely recovered.	Unlikely
36-0631	Bronchospasm/completely recovered.	Unlikely

[1] Data sources: [IND 44,535; 6/22/1998; 8:160-1, 173-88]

[2] WHO preferred term.

[3] This SAE was re-coded from intestinal obstruction to abdominal pain (preferred term).

5.2.4.5.2.5 Discontinuations Due to Adverse Events

One patient with a one-year history of attention deficit disorder was discontinued from the study due to an AE (unusual behavior) judged by the investigator to be of possible relationship to study treatment (budesonide). The AE had not resolved at the patient's final visit. The patient was referred to his primary care physician; follow-up information on the patient's recovery is unavailable. [IND 44,535; 6/22/1998; 8:188]

5.2.4.5.2.6 Adverse Events of Severe Intensity

The incidence of severe AEs was 23% in the budesonide group and 17% in the conventional therapy group. Bronchospasm was the most frequently reported severe AE with an incidence of 6% in the conventional therapy group and 4% in the budesonide group. Respiratory infection occurred in 5% of the patients on conventional therapy and 2% of the patients on budesonide. All other severe AEs were reported with incidences of ≤3% in any treatment group. All severe AEs were judged by the investigators to be unlikely causally-related to treatment, except for one event (bronchospasm) in the conventional therapy group which was judged to be possibly causally-related to treatment. [IND 44,535; 6/22/1998; 8:162-70]

5.2.4.5.3 Assessment of HPA-Axis

[IND 44,535; 6/22/1998; 8:64-6, 231-6]

Between the two treatment groups, there were no significant differences in adjusted mean changes in ACTH-stimulated cortisol levels from baseline or in the percentages of patients showing a shift in ACTH-stimulation tests from normal responsiveness at baseline to abnormal responsiveness at Week 52.

Reviewer's Comments: 1. In both treatment groups the mean increase in cortisol levels after ACTH-stimulation were decreased at Week 52 compared to the baseline, suggesting a measurable systemic effect of inhaled corticosteroids in both groups. 2. The adjusted mean changes in ACTH-stimulated cortisol levels from baseline to Week 52 were numerically more negative in patients on budesonide compared to those on conventional therapy. This suggests that patients on budesonide had more HPA-axis suppression than those on conventional therapy.

Table 5.2.4.5.3.A. Summary Results of ACTH-Stimulation Tests for Patients Who Completed One Year of Open-Label Treatment.[1]

Variable		Open-Label Treatment	
		Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Cortisol Levels (nmol/L)			
All patients:			
Basal:	Baseline	324	287
	Week 52	306	293
		(n=30)	(n=68)
ACTH-Stimulated:	Baseline	585	642
	Week 52	568	578
		(n=31)	(n=67)
Male Patients:			
Basal:	Baseline	309	272
	Week 52	284	303
		(n=22)	(n=46)
ACTH-Stimulated:	Baseline	586	623
	Week 52	562	550
		(n=22)	(n=45)
Female Patients:			
Basal:	Baseline	366	317
	Week 52	366	272
		(n=8)	(n=22)
ACTH-Stimulated:	Baseline	584	681
	Week 52	583	634
		(n=9)	(n=22)
Adjusted Mean Changes in ACTH-Stimulated Cortisol Levels from Baseline[2] (p-value vs. conventional asthma therapy)			
All Patients		-53.0	-99.7 (p=0.278)
Male Patients		-75.9	-118.0 (p=0.490)
Female Patients		-7.0	-93.7 (p=0.144)

[1] Data source: [IND 44,535; 6/22/1998; 8:231]
[2] Means adjusted for Center Effect.

Table 5.2.4.5.3.B. 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.[1,2]

ACTH Stimulation Test[3]	Baseline	Open-Label Treatment			
		Conventional Asthma Therapy		Budesonide Nebulizing Suspension	
		Abnormal	Normal	Abnormal	Normal
All Patients	Abnormal	0 (0%)	4 (100%)	2 (29%)	5 (71%)
	Normal	5 (19%)	21 (81%)	10 (17%)	49 (83%)
Male Patients	Abnormal	0 (0%)	3 (100%)	2 (29%)	5 (71%)
	Normal	4 (21%)	15 (79%)	8 (21%)	30 (79%)
Female Patients	Abnormal	0 (0%)	1 (100%)	0 (0%)	0 (0%)
	Normal	1 (14%)	6 (86%)	2 (10%)	19 (90%)

[1] Data source: [IND 44,535; 6/22/1998; 8:232]

[2] Total n for each treatment group was based on patients with non-missing ACTH and basal cortisol data at baseline and Week 52.

[3] 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.

5.2.4.5.4 *Evaluation of Clinical Laboratory Tests*

[IND 44,535; 6/22/1998; 8:62-3, 190-207]

In general, the differences between the test value means at baseline and the last visit for any laboratory test variable in the same treatment group as well as the differences between the two treatment groups in mean values for any laboratory test variable were similar. The number of clinically significant shifts to values above or below baseline was relatively small. There were no apparent differences in the shifts between the two treatment groups.

Also, there were no apparent differences between the two treatment groups in the distribution or incidence of clinically significant test value abnormalities. Overall, the number of clinically significant laboratory test value abnormalities was low, all abnormal values occurred at an incidence of <3%, and many were present at baseline. In most cases the investigator attributed the abnormal test values to concomitant diseases such as allergy or viral infections.

5.2.4.5.5 *Vital Signs and Physical Findings*

[IND 44,535; 6/22/1998; 8:63-4, 220-30]

There were no clinically relevant changes in any vital sign variable from baseline to the last observation for either treatment group. There were no clinically relevant differences in the shift rates from normal to abnormal physical findings between two treatment groups. The most frequently observed physical examination abnormality was nasal/sinus discharge.

5.2.4.5.6 *Assessment Of Oral Fungal Cultures*

[IND 44,535; 6/22/1998; 8:66, 237-9]

The incidence of clinically significant abnormalities in oral fungal cultures in the budesonide group (4%) was slightly higher than that of the conventional therapy group (2%).

5.2.4.5.7 *Assessment of Body Length/Height (Stadiometry)*

[IND 44,535; 6/22/1998; 8:66-70, 195-207]

For patients who completed the 12-month treatment period, the mean measured growth velocity (cm/year) of patients on conventional therapy was numerically smaller than that of patients on budesonide (0.75, 0.98 and 0.44 cm/year for all patients, male patients, and female patients, respectively).

Table 5.2.4.5.7A. 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.

Stratification Group	Treatment Group	n	Mean Measured Growth Velocity[1]
All Patients	Budesonide	167	6.96±2.34
	Conventional	72	6.21±2.43
Male Patients	Budesonide	100	7.24±2.30
	Conventional	51	6.26±2.09
Female Patients	Budesonide	67	6.55±2.35
	Conventional	21	6.11±3.16

[1] The differences between 2 treatment groups were not statistically different ($p>0.05$ for all patients, males, or females).

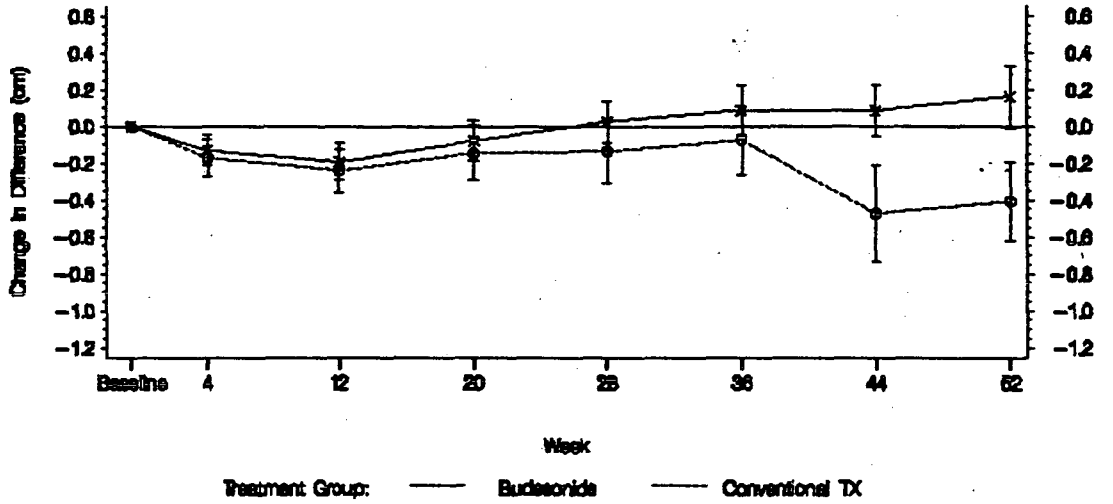
Data source: [IND 44,535; 6/22/1998; 8:250-1]

A similar result was observed in the mean changes from baseline in the difference between observed heights and standard median height (50th percentile based on data from the U.S. National Center for Health Statistics) for all the patients who completed the open-label treatment phase (Figure 5.2.4.5.7).

Of note, at baseline the mean height for all randomized patients was 107.1 cm and 108.2 cm in the budesonide and conventional treatment groups, respectively. However, among patients who completed the 12-month treatment period, the mean observed height was 106.3 cm and 111.2 cm in the budesonide and conventional treatment groups, respectively. One reasonable explanation for these observations is the differentially higher dropout rate in younger children in the conventional therapy group. The dropout rate in children aged two years or less was significantly higher in the conventional therapy group (56.3%) compared to the budesonide group (11.2%). Thence, the mean and median age (years) of study discontinuations were lower in the conventional therapy

group (4.2 and 3.3 years, respectively) compared to the budesonide group (5.3 and 5.3 years, respectively).

Figure 5.2.4.5.7. The Mean (±Standard Error) Changes from Baseline in the Difference between Observed Heights and Standard Median Height for all the Patients Who Completed One Year of Open-Label Treatment. [IND 44,535; 6/22/1998; 8:68]



The shifting patterns in observed height relative to standard 50th percentile height from baseline to Week 52 were similar in both groups.

Table 5.2.4.5.7B. Shifts in Observed Height Relative to Standard 50th Percentile Height from Baseline to Week 52 for All Patients Who Completed One Year of Open-Label Treatment.

Parameter	Baseline	Week 52			
		Conventional Asthma Therapy		Budesonide Nebulizing Suspension	
		Below	Above	Below	Above
Observed Height[1]	Below	23 (88.5%)	3 (11.5%)	69 (88.5%)	9 (11.5%)
	Above	7 (14.9%)	40 (85.1%)	7 (7.1%)	92 (92.9%)

[1] Relative to the standard 50th percentile height based on data from the U.S. National Center for Health Statistics for age and gender.
Data source: [IND 44,535; 6/22/1998; 8:249]

Reviewer's Comments: The problems in the assessment of growth velocity in this study were similar to those in Study 3072B. 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. Re-randomization between double-blind (12-week) and open-label (52-week) phases without washout period. 4. Significant portion of patients had various intervals between the end of double-blind phase and the beginning of open-label phase. 5. The use of inhaled steroids in the conventional

therapy group. 6. The use of oral steroids for acute asthma exacerbation. Thence, it's hard to interpret the growth data and the significance of these data is uncertain.

Importantly, the dropout rate in children aged two years or less was significantly higher in the conventional therapy group (56.3%) compared to the budesonide 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 budesonide group. (Section 5.2.4.4.1)

5.2.4.5.8 *Assessment of Skeletal Age*

[IND 44,535; 6/22/1998; 8:70, 253]

There were no consistent patterns in changes of the mean differences between measured skeletal age and chronological age from baseline to Week 52 either between the two treatment groups or among different subsets of patients (male or female patients) in the same treatment group.

Table 5.2.4.5.8. Summary of Mean Differences Between Skeletal Age and Chronological Age (in Years) Over One Year (Week 0 to Week 52) for Patients Who Completed One Year of Open-Label Treatment.

Stratification Group	Treatment Group	Time Interval	n	Mean Difference[1]
All Patients	Budesonide	Baseline	173	0.27±0.77
		Week 52	167	0.23±0.87
	Conventional	Baseline	72	0.16±0.85
		Week 52	71	0.09±0.91
Male Patients	Budesonide	Baseline	69	0.25±0.77
		Week 52	68	0.28±0.88
	Conventional	Baseline	22	0.31±0.82
		Week 52	22	0.38±1.01
Female Patients	Budesonide	Baseline	104	0.28±0.77
		Week 52	99	0.19±0.87
	Conventional	Baseline	50	0.09±0.87
		Week 52	49	-0.03±0.84

[1] Measured skeletal age minus chronological age.

Data source: [IND 44,535; 6/22/1998; 8:253]

5.2.5 Conclusions and Comments of Study Results

This was a randomized, open-label, active-controlled, 52-week extension of a previous 12-week, randomized, double-blind, placebo-controlled study to assess the long-term safety in asthmatic children aged 6 months to 8 years whose asthma was controlled with titrated doses budesonide nebulizing suspension or conventional asthma therapies (that could have included inhaled GCS, β_2-agonists, methylxanthines and non-steroidal anti-inflammatories).

The results demonstrated that patients on budesonide and those on conventional asthma therapy had similar improvements in most efficacy variables. Between the two treatment groups no statistically significant difference was observed in the mean changes from baseline in asthma symptom scores, use of breakthrough medication, or pulmonary function. The proportion of patients that used oral prednisone and the average total daily amount used were slightly higher in the conventional therapy group. (Table 5.2.5)

In general, the safety evaluations did not reveal apparent difference between the two treatment groups in reported adverse events or regular clinical laboratory tests. After adjusting for length of time in the study, there were no obviously significant differences in the type, incidence, or severity of AEs between treatment groups. The relative risks of vomiting, urticaria, and eaache were higher (>2) in the budesonide group compared to the conventional asthma therapy group. The significance of these observations was not clear. Of note, psychiatric disorders and use of psycholeptics were reported more frequently in the budesonide group than in the conventional therapy group. Similar findings were observed in Study 04-3072B. In both treatment groups the mean increase in cortisol levels after ACTH-stimulation were decreased at Week 52 compared to the baseline, suggesting a measurable systemic effect of inhaled corticosteroids in both groups. The adjusted mean changes in ACTH-stimulated cortisol levels from baseline to Week 52 were numerically more negative in patients on budesonide compared to those on conventional therapy, suggesting that patients on budesonide had more HPA-axis suppression than those on conventional therapy. The incidence of clinically significant abnormalities in oral cavity fungal cultures was marginally higher in the budesonide groups (4%) compared to the conventional therapy group (2%).

In this study, the growth velocity of patients on conventional asthmatic therapy was numerically (0.75 cm/year) smaller than that of patients on budesonide. These data are hard to interpret due to problems in the study design, that were similar to those in Study 04-3072. These included the following: 1. Treatments were not blinded. 2. Baseline growth velocity of each patient was not assessed. 3. Re-randomization between double-blind and open-label phases without washout period. 4. Significant proportion of patients had various intervals between the end of double-blind phase and the beginning of open-label phase. 5. The use of inhaled steroids in the conventional therapy group. 6. The use of oral steroids for acute asthma exacerbation. Thence, the significance of these data is uncertain. Importantly, the dropout rate in children aged two years or less was significantly higher in the conventional therapy group (56.3%) compared to the budesonide 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 budesonide group. All these may explain, at least partially, why the mean measured growth velocity was smaller in the conventional therapy group.

Table 5.2.5. Mean changes from baseline in efficacy variables.

Mean Change from Baseline[1] (Week 0-52)	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Asthma Symptom Score:		
Nighttime	-0.08	-0.10
95% CI	-0.19, 0.03	-0.19, -0.02
Daytime	-0.10	-0.09
95% CI	-0.22, 0.01	-0.18, 0.00
Use of Breakthrough Medication:		
Days	-1.0	-0.5
95% CI	-1.9, -0.1	-1.2, 0.2
Nebulizations (of Nebulizer)/day	0.07	-0.02
95% CI	-0.1, 0.3	-0.2, 0.1
Puffs (of pMDI)/day	-0.25	-0.03
95% CI	-0.7, 0.2	-0.4, 0.3
PEF (L/min):		
Morning	8.3	8.6
95% CI	-13.1, 29.9	-7.1, 24.4
Evening	8.5	12.0
95% CI	-13.1, 30.0	-3.9, 27.9
Spirometry:		
FEV_1 (L/min)	0.07	0.06
95% CI	-0.05, 0.18	-0.03, 0.14
FVC (L/min)	0.13	0.08
95% CI	-0.03, 0.28	-0.03, 0.19
$FEF_{25-75\%}$	0.00	0.04
95% CI	-0.17, 0.17	-0.08, 0.17
Proportion of Patients Discontinued due to Worsening Asthma	<1%	<1%
Prednisone Use:		
Number (%) of Patients that Used Oral Prednisone During the Study:		
No	47 (46%)	99 (49%)
Yes	56 (54%)	105 (51%)
Average Total Daily Amount Used (mg):		
Mean±SD	0.63±0.97	0.58±1.38
Median	0.24	0.11

[1] For those patients who were able to perform the test.
Data sources: Tables 5.2.4.1B, 5.2.4.4.1-4.

6. INTEGRATED SUMMARY OF SAFETY (ISS)

6.1 Introduction

The original NDA, submitted on November 17, 1997, included the Integrated Summary of Safety (ISS). The data cutoff date for the original ISS was April 15, 1997. The NDA resubmission (August 7, 1998) included the updated ISS that presented new safety information received in the reporting period of April 16, 1997 through February 28, 1998. During this period, 5 studies were completed: 2 U.S. long-term open-label studies (04-3072B & 04-3100B), 2 Non-U.S. studies for indications other than persistent asthma (04-9294 & SD-004-0076), and a South African compassionate use program.

In response to the Agency's comments in the approval letter dated May 20, 1998 on the original NDA submission, the sponsor has accepted the Agency's position that

The original NDA review included a review of the original ISS (Original Review: Section 10). In this section the comparative adverse event information excluding patients under one year of age or patients randomized to 1.0 mg BID treatment in three U.S. 12-week pivotal studies will be reviewed first. Then, the combined safety profile of Pulmicort Respules demonstrated in three 52-week open-label studies will be assessed.

6.2 U.S. Clinical Studies

6.2.1 *Three U.S. Randomized, Controlled, Double-Blind, 12-Week, Pivotal Studies (04-3069, 04-3072, 04-3100)*

Data of three pivotal studies excluding patients under one year of age or patients randomized to 1.0 mg BID treatment are reviewed in this section.

6.2.1.1 Reported Adverse Events

[8/7/1998; 8:21-5, 230-8]

In general, the incidence of adverse events was comparable between the placebo and Pulmicort Respules group. Among adverse events with an incidence of ≥1% in the total 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.

Among adverse events with an incidence of <1% in the Pulmicort Respules group, the AEs belonging to the following disorders (WHO body system) occurred more frequently in the Pulmicort Respules group: as a whole – general disorders, skin and appendages disorders,

vision disorders, psychiatric disorders, application site disorders, and urinary system disorders.

Table 6.2.1.1: Adverse Events with an Incidence of ≥ 3% in Any of the Pulmicort Respules Groups by Body System and Preferred Term (Includes all Pulmicort Respules Dose Groups). Data are Pooled from the Three U.S. Pivotal Pulmicort Respules Studies Excluding Patients Who Were Less Than One Year of Age or Who Were Randomized to 1.0 mg BID Treatment (N=945).
[8/7/1998; 8:22]

	Placebo (N=227)	Total Pulmicort Respules (N=718)	Pulmicort Respules Total Daily Dose		
			0.25 mg (N=178)	0.5 mg (N=223)	1.0 mg (N=317)
Respiratory System Disorders					
Respiratory Infection	82 (36%)	259 (36%)	60 (34%)	79 (35%)	120 (38%)
Sinusitis	38 (17%)	96 (13%)	22 (12%)	27 (12%)	47 (15%)
Rhinitis	21 (9%)	74 (10%)	13 (7%)	24 (11%)	37 (12%)
Coughing	12 (5%)	52 (7%)	9 (5%)	19 (9%)	24 (8%)
Pharyngitis	15 (7%)	41 (6%)	7 (4%)	13 (6%)	21 (7%)
Bronchospasm	15 (7%)	27 (4%)	9 (5%)	8 (4%)	10 (3%)
Bronchitis	13 (6%)	25 (3%)	4 (2%)	11 (5%)	10 (3%)
Body as a Whole-General Disorders					
Fever	52 (23%)	132 (18%)	31 (17%)	42 (19%)	59 (19%)
Accident and/or Injury	18 (8%)	56 (8%)	17 (10%)	16 (7%)	23 (7%)
Pain	6 (3%)	21 (3%)	5 (3%)	5 (2%)	11 (3%)
Resistance Mechanism Disorders					
Otitis Media	26 (11%)	73 (10%)	22 (12%)	24 (11%)	27 (9%)
Infection Viral	6 (3%)	28 (4%)	8 (4%)	11 (5%)	9 (3%)
Moniliasis	5 (2%)	28 (4%)	8 (4%)	7 (3%)	13 (4%)
Gastro-Intestinal System Disorders	9 (4%)	38 (5%)	9 (5%)	12 (5%)	17 (5%)
Gastroenteritis	7 (3%)	25 (3%)	4 (2%)	8 (4%)	13 (4%)
Vomiting	5 (2%)	21 (3%)	7 (4%)	8 (4%)	6 (2%)
Diarrhoea	5 (2%)	19 (3%)	6 (3%)	5 (2%)	8 (3%)
Abdominal Pain					
Central and Peripheral Nerve System Disorders					
Headache	19 (8%)	52 (7%)	11 (6%)	18 (8%)	23 (7%)
Skin and Appendages Disorders					
Rash	6 (3%)	16 (2%)	1 (<1%)	8 (4%)	7 (2%)
Hearing and Vestibular Disorders					
Ear Infection, NOS*	10 (4%)	29 (4%)	4 (2%)	9 (4%)	16 (5%)
Platelet, Bleeding, and Clotting Disorders					
Epistaxis	3 (1%)	21 (3%)	4 (2%)	[redacted](4%)	9 (3%)
Vision Disorders					
Conjunctivitis	4 (2%)	17 (2%)	1 (<1%)	10 (4%)	6 (2%)

Data Source: [8/7/1998; 8:230-8]
*: NOS: Not otherwise specified.

6.2.1.1.1 *Adverse Events by Daily Dose*

[8/7/1998; 8:22, 230-8]

A dose-related increase in the incidence was observed in the following AEs: respirtory infection, rhinitis, pharyngitis, hyperkinesia, urticaria, and ear infection.

6.2.1.1.2 *Adverse Events by Gender*

[8/7/1998; 8:23, 239-54]

Incidences of AEs were generally similar for male and female patients.

6.2.1.1.3 *Adverse Events by Age*

[8/7/1998; 8:24-5, 255-73]

In general, there was no apparent effect of age on the incidences of most AEs. Adverse events, that occurred most frequently in patients aged ≥1 - <2 years and on Pulmicort Repules included the following: rhinitis, parasitosis, eczema, pustular rash, earache, anorexia, and increase alkaline phosphatase.

6.2.2 *Three U.S. Randomized, Controlled, Open-label, 52-Week Trial Extensions (04-3069B, 04-3072B, 04-3100B) to Three U.S. 12-Week Pivotal Studies*

All three were randomized, 52-week, open-label studies that compared the safety profile of Pulmicort Repules to conventional asthma therapy in patients who previously completed the US pivotal studies. A total of 670 pediatric patients participated in these studies.

6.2.2.1 Patient Demographics and Baseline Characteristics

Age, weight, height, asthma symptom scores, and number of day of breakthrough medicine use were higher and FEV_1% was lower in the conventional asthma therapy group than in the Pulmicort Respules group.

Table 6.2.2.1: Patient Demographics and Baseline Characteristics. Data are Pooled from the Three U.S. Open-Label Pulmicort Respules Studies (N=670).

	Conventional Asthma Therapy	Pulmicort Respules
Demographics	(N=223)	(N=447)
Gender		
Male	142 (63.7%)	291 (65.1%)
Female	81 (36.3%)	156 (34.9%)
Race		
Caucasian	165 (74.0%)	357 (79.9%)
Black	35 (15.7%)	60 (13.4%)
Hispanic	17 (7.6%)	21 (4.7%)
Asian	0 (0%)	2 (0.4%)
Other	6 (2.7%)	7 (1.6%)
Age (months)		
Mean ±SD	63.0±27.8	60.9±25.9
Range	11-112	8-113
6 mos - <1 yr	1 (0.4%)	4 (0.9%)
≥ 1- < 2 yrs	25 (11.2%)	33 (7.4%)
≥2 - < 4 yrs	42 (18.8%)	106 (23.7%)
≥ 4 yrs	155 (69.5%)	304 (68.0%)
Weight (kg)		
N	223	446
Mean ± SD	21.3±8.4	20.7±7.7
Range	8.6-58.9	7.7-76.6
Height (cm)		
N	222	443
Mean ± SD	110.4±17.8	109.1±16.5
Range	72.0-150.1	68.6-155.3
Daytime Asthma symptom Scores (0-3)		
N	196	431
Mean ± SD	0.91±0.68	0.67±0.6
Range	0-3	0-2.82
Nighttime Asthma symptom Scores (0-3)		
N	197	436
Mean ± SD	0.83±0.68	0.63±0.59
Range	0-2.88	0-2.79
% of Predicted FEV_1 (L)		
N	96	184
Mean ±SD	83.42±17.31	84.16±18.20
Range		
# of days Use of Breakthrough Medicine		
N	197	436
Mean ± SD	7.6±8.4	4.8±7
Range	0-30	0-48

Data Source: [8/7/1998; 9:4-8]

6.2.2.2 Duration of Exposure to Treatment

The mean duration of treatment in the Pulmicort Respules group was longer than the conventional therapy group.

Table 6.2.2.2: Duration of Exposure. Data are Pooled from the Three U.S. Open-Label Pulmicort Respules Studies (N=670).

Duration of Treatment (Days)	Conventional Asthma Therapy (N=223)	Pulmicort Respules (N=447)
Mean ± SD	304±119	342±83
Median	365	365
25% Percentile	274	362
75% Percentile	371	371

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

6.2.2.3 Reported Adverse Events

[8/7/1998; 8:64-7, 85-8]

The proportion of patients experiencing adverse events was higher in the Pulmicort Respules group than in the conventional therapy (including inhaled steroids) group. However, the increased average duration of exposure for the Pulmicort Respules patients should be taken into account.

As expected, the incidences of all AEs, except epistaxis, were higher in the 1-year open-label phase than the 12-week double-blind phase.

Table 6.2.2.3A: Summary of Reported Adverse Events in the Three U.S. Open-Label Pulmicort Respules Studies (N=670).

	Conventional Asthma Therapy (N=223)	Pulmicort Respules (N=447)
No. of Patients with an AE	184 (83%)	416 (93%)
No. of Patients with a Serious AE	18 (8.1%)	37 (8.3%)
No. of Patients Who Discontinued from the Study Due to an AE	1 (0.4%)	3 (0.7%)

Data Source: [8/7/1998; 9:10-18, 147-51]

Without taking the increased average duration of exposure for the Pulmicort Respules patients into account, the reported incidences for most AEs appeared higher in the Pulmicort Respules group. After adjusting for the length of time in the study, the incidences of reported AEs with an incidence of ≥3% were not significantly different between the two treatment 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. (Table 6.2.2.3B) There was no apparent difference in the incidences of psychiatric AEs between the two treatment groups. [8/7/1998; 9:16]

Table 6.2.2.3B: Adverse Events with an Incidence of ≥3% in the Pulmicort Respules Group by Body System and Preferred Term with Relative Risks (From Proportional Hazards Model) and 95% Confidence Limits, and Adjusted for Length of Time (Per 12 Patient-Months) (Studies 04-3069B, 04-3072B, 04-3100B) (N=670).

	Open-Label Treatment		Relative Risk	95% Confidence Interval	Frequency per 12 Pt-Months	
	Conventional Asthma Therapy (N=223)	Pulmicort Respules (N=447)			Conventional Asthma Therapy	Pulmicort Respules
Respiratory System Disorders						
Respiratory Infection	109 (49%)	259 (58%)	1.058	(0.85, 1.32)	0.6	0.6
Sinusitis	60 (27%)	147 (33%)	1.085	(0.80, 1.47)	0.3	0.4
Pharyngitis	38 (17%)	87 (19%)	0.969	(0.66, 1.42)	0.2	0.2
Rhinitis	24 (11%)	76 (17%)	1.441	(0.91, 2.28)	0.1	0.2
Bronchitis	17 (8%)	50 (11%)	1.262	(0.73, 2.19)	0.1	0.1
Coughing	13 (6%)	37 (8%)	1.260	(0.67, 2.37)	0.1	0.1
Pneumonia	16 (7%)	32 (7%)	0.862	(0.47, 1.57)	0.1	0.1
Bronchospasm	17 (8%)	28 (6%)	0.689	(0.38, 1.26)	0.1	0.1
Stridor	9 (4%)	15 (3%)	0.708	(0.31, 1.62)	0.1	0.0
Body as a Whole						
Fever	45 (20%)	124 (28%)	1.111	(0.72, 1.72)	0.2	0.2
Accident and/or Injury	28 (13%)	72 (16%)	1.279	(0.91, 1.80)	0.3	0.3
Flu-Like Disorder	7 (3%)	24 (5%)	1.412	(0.61, 3.29)	0.0	0.1
Pain	10 (4%)	18 (4%)	0.769	(0.36, 1.67)	0.1	0.0
Resistance Mechanism Disorders						
Otitis Media	42 (19%)	97 (22%)	1.010	(0.70, 1.45)	0.2	0.2
Infection Viral	27 (12%)	41 (9%)	0.631	(0.39, 1.03)	0.2	0.1

	Open-Label Treatment		Relative Risk	95% Confidence Interval	Frequency per 12 Pt-Months	
	Conventional Asthma Therapy (N=223)	Pulmicort Respules (N=447)			Conventional Asthma Therapy	Pulmicort Respules
Moniliasis	6 (3%)	27 (6%)	1.988	(0.82, 4.82)	0.0	0.1
Varicella	6 (3%)	21 (5%)	1.481	(0.60, 3.68)	0.0	0.1
Hearing & Vestibular Disorders						
Ear Infection NOS	24 (11%)	58 (13%)	1.034	(0.64, 1.66)	0.1	0.1
Earache	1 (<1%)	12 (3%)	4.936	(0.64, 38.0)	0.0	0.0
Central & Peripheral Nervous Sys. Disorder						
Headache	23 (10%)	51 (11%)	0.964	(0.59, 1.58)	0.1	0.1
Gastro-Intestinal System Disorders						
Gastroenteritis	16 (7%)	44 (10%)	1.189	(0.67, 2.11)	0.1	0.1
Vomiting	11 (5%)	37 (8%)	1.460	(0.74, 2.86)	0.1	0.1
Abdominal Pain	16 (7%)	26 (6%)	0.688	(0.37, 1.28)	0.1	0.1
Diarrhoea	9 (4%)	20 (4%)	0.943	(0.43, 2.07)	0.1	0.0
Nausea	6 (3%)	13 (3%)	0.926	(0.35, 2.44)	0.0	0.0
Skin & Appendages Disorders						
Rash	11 (5%)	31 (7%)	1.244	(0.63, 2.48)	0.1	0.1
Urticaria	9 (4%)	18 (4%)	0.854	(0.38, 1.90)	0.1	0.0
Eczema	5 (2%)	16 (4%)	1.409	(0.52, 3.85)	0.0	0.0
Vision Disorders						
Conjunctivitis	11 (5%)	33 (7%)	1.332	(0.67, 2.64)	0.1	0.1

Data Source: [8/7/1998; 9:19-20]