Table 8.3.4.4.3A . Summary results of ACTH-simulated cortisol tests.[1] [52:63]

Variable		Placebo	Budesonide Nebulizing Suspension, BID		
			0.25 mg	0.5 mg	1.0 mg
ACTH Stimulated Cortisol Levels (nmol/L)	n				
Basal		8	14	11	13
ACTH-Stimulated		8	14	11	13
Basal:	Baseline	248	220	248	241
	Week 12	261	258	237	257
ACTH Stimulated:	Baseline	654	637	582	602
	Week 12	631	675	633	555
Adjusted Mean Change in ACTH-Stimulated Cortisol Levels from Baseline[2]		-9.1	41.2	54.7	-56.3
	(p-value vs. placebo)		(0.337)	(0.241)	(0.390)

[1] Data source: [52:229; Section 14.3.5, Table 4]
[2] Means adjusted for Center Effect.

Table 8.3.4.4.3B. Shifts in ACTH stimulation test from baseline to double-blind treatment phase (Week 12).[1,2] [52:63]

Parameter	Base-line	Placebo n=8		Budesonide Nebulizing Suspension mg BID 0.25 n=14		0.5 n=11		1.0 n=13	
		Abn	Norm	Abn	Norm	Abn	Norm	Abn	Norm
ACTH Stimulation Test[3]	Abn	-	1	1	2	_	1	-	2
	Norm	-	7	2	9	1	9	1	10

[1] Data source: [52:230; Section 14.3.5, Table 5]
[2] Total n for each treatment group was based on patients with non-missing ACTH and basal cortisol data at baseline and Week 12.
[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.

8.3.4.4.4 Evaluation of Clinical Laboratory Tests

[52:60-1]

Overall, the number of clinically significant laboratory test value abnormalities was low. There were no apparent differences between treatment groups in the distribution or incidence of clinically significant test value abnormalities. 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 placebo and budesonide groups. The majority of clinically significant values were judged by the investigator to be unrelated to study treatment and due to concomitant diseases such as viral infections or allergic

rhinitis. In a few cases an explanation could not be found. [52:186-219]

8.3.4.4.5 *Vital Signs and Physical Findings*

There were no clinically relevant changes in any vital sign variable from baseline to the 12-week treatment phase for any treatment group. There were no apparent differences in the shift rates from normal to abnormal physical findings during treatment between any of the treatment groups. The most frequently observed physical abnormalities were in the respiratory system, with nasal and sinus discharge being the most frequent. [52:221-8]

8.3.4.4.6 *Assessment Of Oral And Nasal Fungal Cultures*

There were no apparent differences between treatment groups in changes in oral cavity fungal cultures from the baseline to Week 12. However, the incidence of clinically significant abnormalities in oral cavity fungal cultures in the placebo group (0%) was lower than that of the budesonide groups (7%); 6 (13%) patients in the 0.5 mg BID group and 3 (7%) patients in the 1.0 mg BID group. [52:233-5]

8.3.5 *Conclusions and Comments of Study Results*

This study of budesonide nebulizing suspension twice a day was performed in young children aged four to eight years who had been using inhaled corticosteroids prior to randomization for the control of their asthma symptoms.

The results demonstrated that budesonide improved both the primary and secondary efficacy variables compared to placebo (Table 8.3.5). These improvements were not dose-dependent. All three budesonide regimens significantly improved the nighttime and daytime asthma symptom scores, reduced the use of breakthrough medication (short-acting inhaled bronchodilator), and decreased the proportion of patients who were discontinued from the study. After adjusting for multiple comparisons using Dunnett's test, only 0.5 mg BID regimen no longer demonstrated significant improvements in primary efficacy variables, i.e., both nighttime and daytime asthma symptom scores. The 0.5 mg BID regimen significantly improved morning PEF, FEV_1 and $FEF_{25-75\%}$. So did the 0.25 mg BID regimen on morning and evening PEFs and the 1.0 mg BID regimen on morning PEF and $FEF_{25-75\%}$. The improvements in PEF and FEV_1 were not parallel.

The safety evaluations did not reveal apparent difference between the treatment groups in reported adverse events, changes in physical examinations, or clinical laboratory tests. Of note, there was a numerical increase in the incidence of coughing, moniliasis, and clinically significant abnormalities in oral cavity fungal cultures in the budesonide groups compared to the placebo. These AEs were not unpredicted in patients using inhaled corticosteroids. In general, the budesonide nebulizing suspension regimens used in this study appeared to be safe. However, the observation that the numerical decrease in the adjusted mean change in ACTH-stimulated cortisol level from baseline was greater in the 1.0 mg BID budesonide group (-56.3 nmol/L) compared to placebo (-9.1 nmol/L) is worrisome (Table 8.3.4.4.3A).

. This possible HPA-axis suppression by budesonide treatment in all pivotal studies will be carefully reviewed in ISS.

Table 8.3.5. Mean changes from baseline in primary and secondary efficacy variables; All Patients Treated, Last Value Carried Forward.[1]

Mean Change from Baseline of Variable (Weeks 0-12)[2]	Placebo	Budesonide Nebulizing Suspension, BID		
		0.25 mg	0.5 mg	1.0 mg
Asthma Symptom Score (scale of 0-3):				
Nighttime	-0.08	-0.36	-0.37	-0.36
(p-value vs. placebo)		(0.022)**	(0.021)*	(0.026)**
Daytime	-0.11	-0.45	-0.53	-0.55
(p-value vs. placebo)		(0.012)**	(0.003)**	(0.002)**
Use of Breakthrough Medicine (days)	-3.14	-5.56	-6.66	-6.00
(p-value vs. Placebo)		(0.032)*	(0.002)*	(0.012)*
PEF (L/min):				
Morning	-1.3	15.3	11.8	10.4
(p-value vs. placebo)		(0.002)*	(0.016)*	(0.030)*
Evening	3.0	14.9	11.6	13.2
(p-value vs. placebo)		(0.042)*	(0.152)	(0.083)
Spirometry:				
FEV_1 (L)	-0.01	0.05	0.08	0.07
(p-value vs. placebo)		(0.155)	(0.043)*	(0.065)
FVC (L)	0.04	0.09	0.06	0.05
(p-value vs. placebo)		(0.292)	(0.607)	(0.751)
$FEF_{25-75\%}$ (L/sec)	-0.06	0.00	0.14	0.14
(p-value vs. placebo)		(0.504)	(0.025)*	(0.023)*
Proportion of Patients Discontinued (%)	43	13	12	20
(p-value vs. placebo)[3]		(0.002)*	(0.002)*	(0.023)*

[1] Data sources: Tables 8.3.4.1, 8.3.4.3.1.1, 8.3.4.3.2.1A, 8.3.4.3.2.3-4.

[2] Mean change adjusted for center effect; except indicated otherwise, the difference between the mean of all measurements during weeks 0-12 and the mean of baseline values is shown.

[3] Using Fisher's exact test.

* Statistically significantly different from placebo at the .05 level before adjusting for multiple comparisons.

** Statistically significantly different from placebo at the .05 level before and after adjusting for multiple comparisons using Dunnett's test (only performed for asthma symptom score).

8.4 Study 04-3069B: A Study of the Safety and Efficacy of Budesonide (Pulmicort) Nebulizing Suspension Compared to Conventional Asthma Therapy Following 52 Weeks of Open-Label Treatment in Children with Asthma Aged Eight Years and Younger.

8.4.1 Objectives

[110:14-5]

This randomized, active-controlled, open-label study was preceded by a randomized, double-blind, placebo-controlled, parallel treatment phase (Study 04-3069) that assessed the efficacy and safety of budesonide nebulizing suspension, 0.25, 0.5 and 1.0 mg QD compared to placebo in 359 children aged six months to eight years with asthma not well-controlled on non-GCS therapies. The primary objective of this 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 β_2-agonists, methylxanthines and inhaled non-steroidal anti-inflammatories, but not inhaled GCS, per the judgment of the investigator).

8.4.1.1 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, vital signs, and clinical laboratory tests (including oropharyngeal and nasal fungal cultures).
- Changes in body length/height (stadiometry).

8.4.1.2 Efficacy Variables

- The mean change from baseline in nighttime and daytime asthma symptom scores over the 52-week treatment phase.
- Patient outcome, including the proportions of patients who were discontinued from the study for any reason and the proportion of patients who were 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 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 PEF.
- Changes in health status measurements, including the Modified Functional Status II Child Health Status Scale and the RAND General Health Index.
- Differences in asthma-related health care utilization and indirect health care measurements.

Reviewer's Comments: It is always difficult in assessing mainly subjective efficacy endpoints in an open-label study without bias.

8.4.2 Design

[110:15-7]

This was a multicenter randomized, open-label, active-controlled, parallel-group study. A total of 272 patients were randomized at 26 centers located throughout the USA.

Patients who successfully completed the 12-week, double-blind treatment phase of Study 04-3069 were eligible to enter this optional 52-week open-label extension phase. There was no washout period between the double-blind and the open-label treatment phases.

Two-thirds of the eligible patients were randomized to budesonide nebulizing suspension. These patients started the open-label treatment phase with 0.5 mg budesonide QD in the morning with attempts made at every visit to reduce the dose to 0.25 mg QD in the morning, followed by 0.25 mg every other day in the morning, 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 by increasing the dose of budesonide (to a maximum dose of 1.0 mg QD in the morning), 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 β_2-agonists, methylxanthines, and/or inhaled 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.

During the 52-week open-label treatment phase, the patients were scheduled to report to the clinic seven times (Visit 7 - Visit 13) to be evaluated similar to the double-blind treatment phase.

Figure 8.4.2. Open-Label Study Design. [110:16]

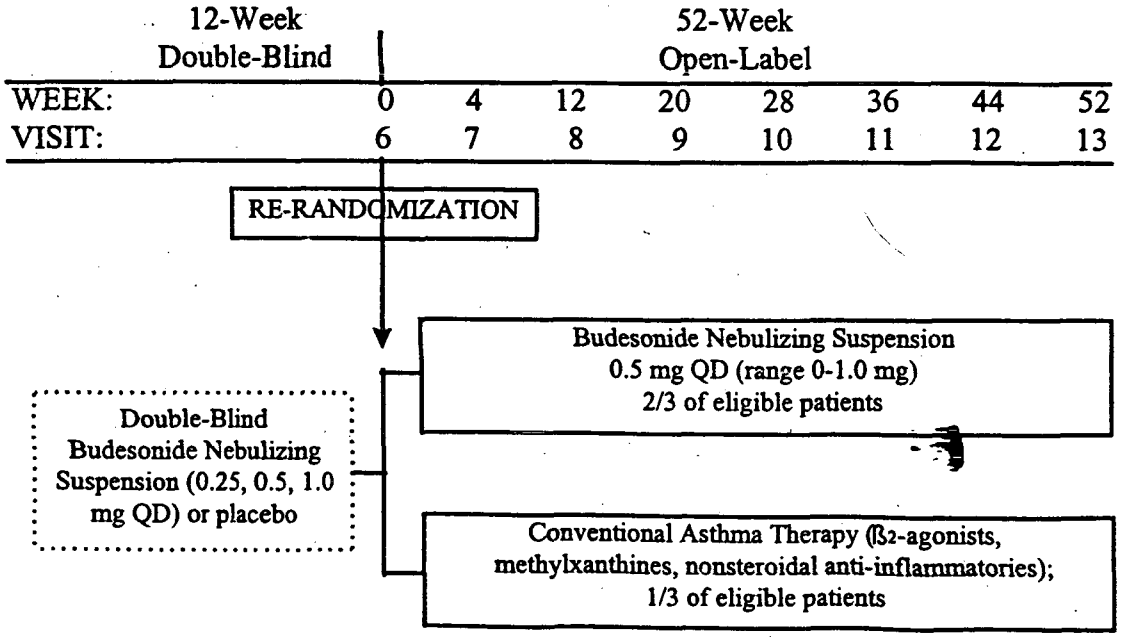


Table 8.4.2. Schedule of Open-Label Visits and Procedures. [110:17]

OPEN-LABEL WEEK NUMBER:	0	4	12	20	28	36	44	52
VISIT NUMBER:	6[a]	7	8	9	10	11	12	13[b]
CLINICAL ASSESSMENTS:								
Comprehensive Physical Examination with Vital Signs	X							X
Brief Physical Examination with Vital Signs		X	X	X	X	X	X	
Body Length/Height (Stadiometry), Weight	X	X	X	X	X	X	X	X
Pulmonary Function Test[c]	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS:								
Hematology, Blood Chemistry	X				X			X
Urinalysis	X				X			X
Basal & Post-ACTH Cortisols[d]	X							X
Oropharyngeal and/or Nasal Fungal Cultures[e]	X							X
OTHER:								
Quality of Life Questionnaire	X	X			X			X
Review Adverse Events	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	
Dispense Study Drug/ Nebulizing Equipment	X	X	X	X	X	X	X	
Dispense New Diaries	X	X	X	X	X	X	X	
Budesonide Output on Filters, Minute Volume, Breaths per Minute		X						

[a] Re-randomization into open-label; new baseline for open-label.

[b] Final visit of open-label.

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

[d] Selected clinical sites only.

[e] Repeated as judged necessary by the investigator.

8.4.3 Protocol

8.4.3.1 Selection of Study Population

[110:18]
Patients who fulfilled the inclusion and exclusion criteria given below were eligible for enrollment into the study.

8.4.3.1.1 Inclusion Criteria

1. The patient completed the 12-week double-blind phase of Study 04-3069. A protocol amendment subsequently allowed patients who discontinued from Study 04-3069 because of the need for oral corticosteroids for worsening airways disease to also be enrolled (this amendment did not apply retroactively).
2. The patient's health would not be compromised by participating in the study, per the judgment of the investigator.

8.4.3.1.2 Exclusion Criteria

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

8.4.3.2 Study Drugs

[110:20]
Same as those in Study 04-3069 (Section 8.2.3.2).

8.4.3.3 Concomitant Treatments

[110:22]
The following medications were not allowed:

- Inhaled GCS (other than study drug)
- Long-acting inhaled β_2-agonists
- Astemizole
- Over-the-counter asthma medications

The following were allowed with the appropriate restrictions:

- Asthma medication: Patients randomized to conventional asthma therapy, could have been treated with 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.

8.4.3.4 Efficacy Measurements and Variables

[101:23-6]
Apart from using a different schedule, the procedures of efficacy measurements in this study were the same as those in Study 04-3069 (Table 8.2.2 and Sections 8.2.3.4-8.2.3.4.2).

8.4.3.5 Safety Measurements and Variables

[101:23-6]

Apart from using a different schedule, the procedures of safety measurements in this study were the same as those in Study 04-3069 (Table 8.2.2 and Sections 8.2.3.5 - 8.2.3.5.2) except the following modifications:

- The patient and/or legal guardian were issued bi-weekly (instead of weekly) diaries and were instructed on the proper way to document health care utilization (Visit 6).

  The health care utilization measurements and indirect economic endpoints related to the patient's asthma were assessed and recorded by the patient's legal guardian every two weeks (instead of every week) during the study.

8.4.3.6 Adverse Events (AEs)

[110:28-30]

Same as those in Study 04-3069 (Sections 8.2.3.6 - 8.2.3.6.3).

8.4.3.7 Treatment and Measurement Discontinuation

[110:18-9]

Same as those in Study 04-3069 (Section 8.2.3.7).

8.4.3.8 Statistical Analysis

[110:32-7]

8.4.3.8.1 Analytical Plan

All patients who were randomized and either completed one year study or discontinued prematurely were included in the tables. For summarization of cortisol and height data, only patients who completed one full year (52 ± 4 weeks) study were summarized.

8.4.3.8.2 Handling of Dropouts

Available data were summarized at each time interval. In addition a last observation was also displayed for all patients regardless of the interval in which it was taken in order to account for dropouts.

8.4.3.8.3 Statistical Methods

For most variables, no formal hypothesis testing was planned. Statistical comparisons using two-sided tests were performed on the difference in adjusted mean changes in ACTH-stimulated cortisol levels from baseline between the budesonide and conventional therapy groups. [110:62] Descriptive statistics were utilized for data summarization. Ninety-five percent confidence intervals (CI) were reported for means within each treatment group.

Baseline data for age, height, weight, diastolic blood pressure, systolic blood pressure, pulse rate, nighttime and daytime asthma symptom scores, morning and evening PEF, FEV_1, FVC and corresponding $FEF_{25-75\%}$ were taken from the last visit of Study 04-0369.

8.4.3.8.3.1 Statistical Methods: Efficacy Variables

8.4.3.8.3.1.1 Nighttime and Daytime Asthma Symptom Scores, Use of Breakthrough Medication, Morning and Evening PEFs (in the subpopulation of patients who were able to perform the tests correctly)

[110:33, 35]

Changes in these variables from the baseline value (Week 0 of this study, mean value of the last 14 days in Study 04-3069) to Weeks 4, 12, 20, 28, 36, 44, 52 and the last observation (mean of values at Weeks 3-4, 11-12, 19-20, 27-28, 35-36, 43-44, 51-52, and last open-label observation, respectively) were evaluated.

8.4.3.8.3.1.2 FEV_1, FVC, and $FEF_{25-75\%}$ (in the subpopulation of patients who were able to perform the tests correctly)

[110:35]

Changes in these variables from the baseline value (last value in Study 04-3069) to Weeks 4, 12, 20, 28, 36, 44, 52 and the last observation (mean of values at Weeks 3-4, 11-12, 19-20, 27-28, 35-36, 43-44, 51-52, and last open-label observation, respectively) were evaluated.

8.4.3.8.3.1.3 Child Health Status, Modified FS-II (R)

[110:34]

Changes in quality of life variables from the baseline value (the last observation in Study 04-3069) to Weeks 4, 28, 52 and the last observation were evaluated. See Section 8.2.3.8.3.1.4 for description of modified Functional Status-II (R) General and Specific scores.

8.4.3.8.3.1.4 Child Health Status Questionnaire, RAND General Health Index

[110:34-5]

Changes in one summary score (RAND-ALL) from the baseline value (the last observation in Study 04-3069) to Weeks 4, 28, 52 and the last observation were evaluated. See Section 8.2.3.8.3.1.5 for description of RAND General Health Index.

Reviewer's Comments: The level of a meaningful change in modified FS-II (R) or RAND score was not provided by the sponsor.

8.4.3.8.3.1.5 Health Resource Utilization Variables and Indirect Economic Endpoints:

[110:35]

Same as those in Study 04-3069 (Section 8.2.3.8.3.1.6).

Reviewer's Comments: No validated instruments for heath status or health resource utilization variables were provided by the sponsor.

8.4.3.8.3.2 Statistical Methods: Safety Variables

[110:35-7]

Analysis of AEs and laboratory variables was performed for all randomized patients. Because of the differences in the exposure time, the incidences of clinical AEs were adjusted for length of time in the study using a proportional hazards model. Analysis of

cortisol (in the subset of patients evaluated) and growth data was only performed for all patients who completed one full year (52±4 weeks) of the study.

Growth velocity over each interval of the open-label extension phase was expressed in terms of centimeters per year and was summarized for each treatment group. Growth velocity over the entire one year open-label extension treatment phase was expressed in terms of centimeters per year.

Additionally, growth over one year of the study was assessed by computing differences between observed height (cm) and standard median height (observed 50th percentile height) based on data from the National Center for Health and Statistics (NCHS). The numbers of patients above or below the standard 50th percentile height were also compared within treatment groups across visits using shift tables.

8.4.4 Results

8.4.4.1 Patient Disposition

[110:37-41]

A total of 272 patients were randomized into the open-label treatment phase of the study (Study 04-3069B), of whom 90 patients were randomized to conventional asthma therapy and 182 patients to budesonide nebulizing suspension. The distribution of the patients by their previous double-blind treatment assignment (Study 04-3069) is shown in Table 8.4.4.1A. Sixty-six (24%) patients had been previously assigned to placebo during double-blind; 206 (76%) had been previously assigned to one of the three budesonide groups (i.e., 0.25, 0.5, or 1.0 mg QD).

Table 8.4.4.1A. Distribution of Randomized Patients by Their Previous Double-Blind Treatment Assignment. [110:38]

Previous Double-Blind Treatment	Open-Label Treatment		Total
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension	
	(n=90)	(n=182)	(n=272)
Placebo	19 (21%)	47 (26%)	66 (24%)
Budesonide Nebulizing Suspension:			
0.25 mg QD	22 (24%)	49 (27%)	71 (26%)
0.5 mg QD	21 (23%)	43 (24%)	64 (24%)
1.0 mg QD	28 (31%)	43 (24%)	71 (26%)

Data Source: [110:70; Section 14.1.1, Table 1]

The disposition of patients enrolled into the open-label treatment phase of the study is summarized in 8.4.4.1B. A total of 54 patients discontinued from the open-label treatment phase of the study. The proportion of patients who discontinued from the study in the conventional asthma therapy group was significantly greater than that for the budesonide

group (32% vs. 14%, respectively; p=0.001). The proportion of patients in the conventional asthma therapy group discontinuing due to worsening asthma (16%) was also greater than for the budesonide group (<1%); this difference was statistically significant (p<0.001).

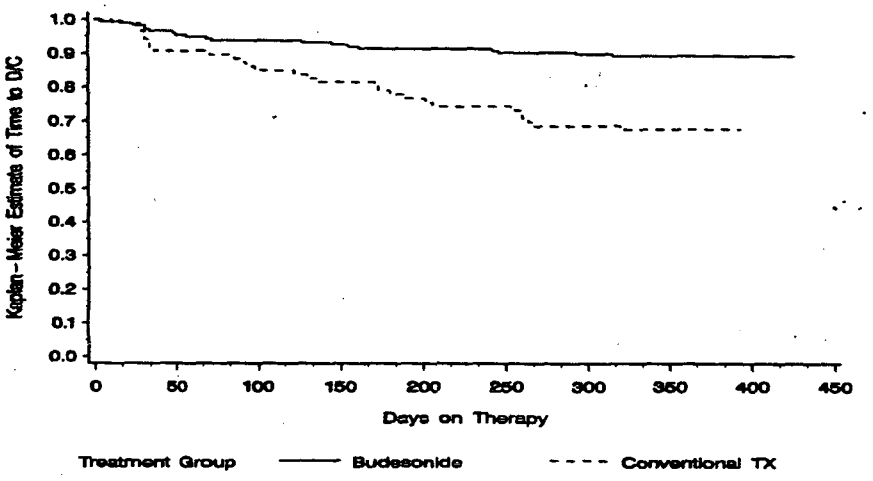
Table 8.4.4.1B. Summary of Patient Disposition.

Patient Disposition	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Randomized	90	182
Completed Open-Label Treatment	61 (68%)	157 (86%)
Total No. Patients Discontinued:	29 (32%)	25 (14%)*
Worsening Asthma[1]	14 (16%)	1 (<1%)*
Adverse Event	1 (1%)	1 (<1%)
Use of Medication Excluded by Protocol[2]	0 (0%)	0 (0%)
Non-Compliance w/Study Procedures	2 (2%)	7 (4%)
Withdrew Consent	12 (13%)	7 (4%)
Lost to Follow-up	0 (0%)	9 (5%)
Evaluated for Efficacy Analyses	90	182
Evaluated for Safety	90	182

[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, e.g., inhaled GCS.
[2] Non-permitted medications for indications other than asthma.
* p≤0.001, versus conventional asthma therapy.
Data Source: [110:73-6; Section 14.1.1, Tables 3 and 4]

A Kaplan-Meier estimate of the time to discontinuation from study therapy (as obtained from start and stop dates of study therapy in the CRF) is shown in Figure 8.4.4.1., which demonstrates that the patients on budesonide remained longer on study therapy compared to those on conventional asthma therapy.

Figure 8.4.4.1. Kaplan-Meier Estimate of Time to Discontinuation From the Study Therapy. [110:41]



8.4.4.2 Demographic and Other Open-Label Baseline Characteristics

[110:41-2]

The basic demographic characteristics of the study population are summarized in Table 8.4.4.2. The basic demographic characteristics were similar for the two treatment groups.

Reviewer's Comments: 1. The proportion of patients who had completed the double-blind phase of the study prior to entering the open-label phase was higher in the budesonide group (86.3%) than the conventional asthma therapy group (64.4%). This might confound the interpretation of the proportion of patients who completed the open-label phase of the study. The proportion of patients who completed the open-label phase of the study was also higher in the budesonide group (86%) than the conventional asthma therapy group (68%) (Table 8.4.4.1B). Of note, in either the budesonide group or the conventional asthma therapy group, the proportion of patients completing the double-blind phase was close to that of the open-label phase. 2. The male to female ratio in this study is typical of asthma patients in this age group.

Table 8.4.4.2. Demographic and Baseline Characteristics. [110:42, 79-80]

Variable	Open-Label Treatment		
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension	Total
n	90	182	272
Gender:			
Male	57 (63.3%)	125 (68.7%)	182 (66.9%)
Female	33 (36.7%)	57 (31.3%)	90 (33.1%)
Age (months):			
Mean ± SD	60.4±26.3	58.4±26.2	59±26.2
Range	11-111	8-111	8-111
Race:			
Caucasian	65 (72.2%)	135 (74.2%)	200 (73.5%)
Black	12 (13.3%)	28 (15.4%)	40 (14.7%)
Hispanic	9 (10.0%)	13 (7.1%)	22 (8.1%)
Oriental	0 (0%)	1 (0.5%)	1 (0.4%)
Other	4 (4.4%)	5 (2.7%)	9 (3.3%)
Weight; Mean ± SD:			
Pounds	44.1±16	43.2±14.5	43.5±15
Kilograms	20.0±7.3	19.6±6.6	19.7±6.8
Height (cm); Mean ± SD	108.1±17.6 (n=89)	106.4±16.5 (n=179)	107±16.9 (n=268)
Double-Blind Phase:			
Completion	58 (64.4%)	157 (86.3%)	215 (79.0%)
Discontinuation	32 (35.6%)	25 (13.7%)	57 (21.0%)

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

[110:43-44, 79-83]

The baseline asthma symptom scores (mean of last two weeks of double-blind phase), spirometry data, PEFs, and breakthrough medication use (last visit of double-blind therapy) are summarized in Table 8.4.4.2.1.

Reviewer's Comments: The budesonide and conventional asthma therapy groups were similar in most variables except the asthma symptom scores and the number of days use of breakthrough medication. Both the mean nighttime and daytime asthma symptom scores as well as the number of days use of breakthrough medication for the patients in the budesonide group were lower or less compared to the conventional asthma therapy group. The effect of this on efficacy and safety variables is uncertain although this may mean that it would be harder to demonstrate an improvement in these variables for the patients assigned budesonide.

Table 8.4.4.2.1. Baseline Lung Function, Asthma Symptom Scores, and Number of Days Use of Breakthrough Medication. [110:44, 79-83]

Variable	Open-Label Treatment		
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension	Total
Nighttime Asthma Symptom Scores:			
Mean±SD	0.80±0.72 (n=81)	0.64±0.59 (n=179)	0.69±0.64 (n=260)
Daytime Asthma Symptom Scores:			
Mean±SD	0.86±0.7 (n=80)	0.69±0.62 (n=178)	0.74±0.65 (n=258)
Spirometry Able:			
No	59 (65.6%)	115 (63.2%)	174 (64.0%)
Yes	31 (34.4%)	67 (36.8%)	98 (36.0%)
PEF Able:			
No	39 (43.3%)	82 (45.1%)	121 (44.5%)
Yes	51 (56.7%)	100 (54.9%)	151 (55.5%)
FEV_1 (L/sec):	1.29±0.35 (n=31)	1.18±0.34 (n=66)	1.21±0.34 (n=97)
FVC (L):	1.62±0.4 (n=31)	1.49±0.43 (n=66)	1.53±0.42 (n=97)
Morning PEF (L/min):	149.4±39.2 (n=50)	151.5±47.8 (n=97)	150.8±45 (n=147)
Evening PEF (L/min):	156.8±42.2 (n=49)	158.8±49.7 (n=97)	158.1±47.2 (n=146)
Number of Days Use of Breakthrough Medication:			
Mean±SD	9.3±9.0 (n=81)	5.5±7.7 (n=179)	6.7±8.3 (n=260)

8.4.4.2.2 Baseline (Visit 6 of Double-Blind Phase) Physical Examination

[110:44, 84-5]

The majority of patients were normal for most physical examination assessments. Approximately half of the patients had abnormalities in the nasal/other examination. The treatment groups were similar with respect to general physical condition at baseline.

8.4.4.2.3 Medications Taken During Open-Label

[110:45-46]

8.4.4.2.3.1 Asthma Medications

Study Medications; General: The mean duration of exposure to the treatment was shorter in the conventional asthma therapy group because patients in the conventional asthma therapy group discontinued from the study earlier than patients in the budesonide group. [110:134-5]

Table 8.4.4.2.3.1A. Duration of Exposure (Days) to Open-Label Treatment.[1] [133:94]

Duration of Treatment (Days)	Budesonide Nebulizing Suspension	Conventional Asthma Therapy
N	176	86
Mean±SD	338±87	293±122
Median	365	365
Minimum	3	11
Maximum	425	393

[1] Six budesonide patients were lost to follow-up and four conventional asthma therapy patients withdrew from open-label after being randomized to conventional asthma therapy.
Data Source: [110:134; Section 14.3.1., Table 1]

Table 8.4.4.2.3.1B. Number of Patients Exposed to Open-Label Treatment by Treatment Month.[1] [133:94]

Treatment	< 3 Months n (%)	>3-<6 Months n (%)	>6-<9 Months n (%)	> 9 Months n (%)	Unknown* n (%)
Budesonide Nebulizing Suspension (N=182)	11 (6%)	4 (2%)	4 (2%)	157 (86%)	6 (3%)
Conventional Asthma Therapy (N=90)	10 (11%)	8 (9%)	9 (10%)	59 (66%)	4 (4%)

[1] Six budesonide patients were lost to follow-up and four conventional asthma therapy patients withdrew from open-label after being randomized to conventional asthma therapy.
Data Source: [110:135; Section 14.3.1., Table 2]

Study Medications; Budesonide Nebulizing Suspension: In patients randomized to budesonide, the average total daily dose of budesonide used during the open-label treatment phase broken down by intervals (between 2 consecutive visits) ranged between 0.52 to 0.54 mg QD. The median daily dose throughout the whole study was 0.5 mg QD. The numbers of patients classified per budesonide dose titration relative to the initial dose of 0.5 mg QD were the following: 108 (59.3%), titrated down and then back up; 27 (14.8%), titrated down and stayed below the initial dose; 24 (13.2%), titrated up and stayed up; and 23 (12.6%), remained on the initial dose throughout the open-label treatment phase. [110:86-7]

Reviewer's Comments: In total, only 2 patients were titrated off and stayed off budesonide treatment (for 114 and 120 days, respectively) until the end of the study. [FA 3/27/98]

Table 8.4.4.2.3.1C. Average Total Daily Dose (mg) of Budesonide Nebulizing Suspension Taken During the Open-Label Phase. [133:93]

	Summary Statistic				
Time Interval	**N**	**Mean**	**Median**	**Minimum**	**Maximum**
Weeks 0-4	182	0.52	0.50	0.250	1.000
Weeks >4-12	175	0.53	0.50	0.188	1.333
Weeks >12-20	167	0.54	0.50	0.125	2.000
Weeks >20-28	164	0.54	0.50	0.063	1.000
Weeks >28-36	162	0.53	0.50	0.000	1.000
Weeks >36-44	159	0.53	0.50	0.000	1.000
Weeks >44	180	0.54	0.50	0.000	1.000

Data Source: [110:86; Section 14.3.1., Table 2]

Study Medications; Conventional Asthma Therapy Medications: In patients randomized to the conventional asthma therapy group, the asthma therapies used were cromoglicic acid (cromolyn sodium; 79%), albuterol (albuterol; 52%), nedocromil (8%), theophylline (6%), beclomethasone (3%) and ipratropium (1%). Albuterol could also have been used as breakthrough medication.

Added Asthma Medications (Concomitant asthma medications): Among asthma medications added during the open-label treatment 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%). [110:89] It should be noted that 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.

8.4.4.2.3.2 Non-Asthma Medications

Concomitant non-asthma medications: In general, the use of concomitant non-asthma medications was similar among treatment groups. Drug classes mentioned most frequently were systemic antibacterials (78%), nasal preparations (64%), other dermatologic preparations (56%), analgesics (53%), cough and cold preparations (33%), and systemic antihistamines (31%). [110:90-2]

8.4.4.3 Measurements of Treatment Compliance

[110:46; 112:145-6]

The proportion of patients who achieved at least 80% compliance with respect to the administration of study drug during the 52-week study period was 82-93% for the budesonide group and 63-89% in the conventional asthma therapy group. The compliance with respect to the study was 77-90% for the budesonide group, and 60-80% in the conventional asthma therapy group.

8.4.4.4 Efficacy Analysis

[110:46-9]

8.4.4.4.1 Asthma Symptoms and Prednisone Use

The mean changes from baseline to the last open-label observation for nighttime and daytime asthma symptom scores were similar, with the 95% CIs overlapping between two groups.

A slightly higher percent of patients from the conventional asthma therapy group (53%) required the use of oral prednisone for their asthma compared to the budesonide group (46%). The mean total daily dose of oral prednisone by the patients in the conventional asthma therapy group was 0.53±0.70, compared to 0.47±0.96 mg for the budesonide treatment group.

Table 8.4.4.4.1. 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. [110:47]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Asthma Symptom Score:[1]		
Mean Change from Baseline		
Nighttime	-0.05	-0.09
95% CI	-0.18, 0.09	-0.19, 0.01
(n)	(81)	(179)
Daytime	-0.09	-0.10
95% CI	-0.23, 0.05	-0.20, 0.00
(n)	(80)	(178)
Prednisone Use:[2]		
Number (%) of Patients that Used Oral Prednisone During the Study:		
No	42 (47%)	98 (54%)
Yes	48 (53%)	84 (46%)
Average Total Daily Amount Used (mg):		
Mean±SD	0.53±0.70	0.47±0.96
Median	0.23	0.00
	(n=90)	(n=182)

[1] Data sources: [110:102-3; Section 14.2, Table 1]
[2] Data sources: [110:107-8; Section 14.2, Tables 4 and 5]

8.4.4.4.2 Breakthrough Medication Use

The mean changes from baseline (last 14 days of double-blind) to the last open-label observation in the number of days use of breakthrough medication and the number of puffs (pMDI) and nebulizations (nebulizer)/day of breakthrough medication were -3.4 days, -0.40 puffs and -0.21 nebulizations, respectively, for the conventional asthma

therapy group and -1.5 days, 0.09 puffs and -0.06 nebulizations for the budesonide group. [110:104-6]

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. For example, despite the higher baseline use of breakthrough medication (9.3±9.0 days) as compared with the budesonide group (5.5±7.7 days), only 63% of patients in the conventional therapy group noted using albuterol on an as-needed basis.

Table 8.4.4.4.2. Mean Changes From Baseline (Last 14 Days Of Double-Blind) to the Last Observation in the Use of Breakthrough Medication. [110:104-6]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Use of Breakthrough Medication:		
Mean Change from Baseline		
Days	-3.4	-1.5
95% CI	-4.6, -2.3	-2.3, -0.7
(n)	(81)	(179)
Nebulizations (of Nebulizer)/day	-0.21	-0.06
95% CI	-0.5, 0.1	-0.2, 0.1
(n)	(40)	(97)
Puffs (of pMDI)/day	-0.40	0.09
95% CI	-1.5, 0.7	-0.8, 1.0
(n)	(22)	(30)

8.4.4.4.3 Morning and Evening PEFs (in the subpopulation of patients who were capable of using peak flow meters):

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

Table 8.4.4.4.3. Mean Changes From Baseline (Last 14 Days Of Double-Blind) to the Last Observation in Morning and Evening PEFs (in the subpopulation of patients who were capable of using peak flow meters). [110:112, 116]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
PEF (L/min):		
Mean Change from Baseline		
Morning	5.9	7.2
95% CI	-8.4, 20.3	[illegible], 18.4
(n)	(50)	[illegible]97)
Evening	6.1	5.9
95% CI	-8.9, 21.2	-5.8, 17.6
(n)	(49)	(97)

8.4.4.4.4 *FEV_1, FVC and corresponding $FEF_{25-75\%}$ (in the subpopulation of patients who could perform consistent Spirometry)*

The FEV_1, FVC and corresponding $FEF_{25-75\%}$ data showed that patients on budesonide nebulizing suspension had similar improvements in pulmonary function when compared to patients on conventional asthma therapy, with the 95% CIs overlapping between the two treatment groups.

Table 8.4.4.4.4. Mean Changes From Baseline (Last 14 Days Of Double-Blind) to the Last Observation in FEV_1, FVC and Corresponding $FEF_{25-75\%}$ (in the subpopulation of patients who were capable of using peak flow meters). [110:113-5]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Spirometry:		
Mean Change from Baseline		
FEV_1 (L/min)	0.05	0.12
95% CI	-0.08, 0.18	0.03, 0.21
(n)	(29)	(63)
FVC (L/min)	0.09	0.14
95% CI	-0.08, 0.26	0.03, 0.25
(n)	(29)	(63)
$FEF_{25-75\%}$	0.05	0.15
95% CI	-0.12, 0.21	0.04, 0.26
(n)	(29)	(63)

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

The data from FS-II (R) General and Specific scores, reflecting the patient's functional status and the relationship of the score to the asthma symptoms, respectively, showed that patients on budesonide had improved health status when compared to patients on conventional therapy.

Reviewer's Comments: The clinical significance of changes in FS-II (R) scores is uncertain particular in an open-label study. The changes in FS-II (R) scores and changes in asthma symptoms scores, PEFs, or the use of breakthrough medication were not parallel, although this is often found for health assessment instruments vs. physiologic measures.

Table 8.4.4.4.5. Mean Changes From Baseline (Last Double-Blind Observation) to the Last Observation in Modified Functional Health Status FS-II (R) General and Specific Scores. [110:109]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
FS-II Scores:		
Mean Change from Baseline		
General	1.1	3.6
95% CI	-2.5, 4.7	0.9, 6.3
(n)	(87)	(175)
Specific	0.8	3.5
95% CI	-2.7, 4.3	0.9, 6.1
(n)	(87)	(175)

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

The RAND-ALL Child Health Status data showed that patients on budesonide had improved health status when compared to patients on conventional therapy.

Reviewer's Comments: The clinical significance of changes in RAND-ALL scores is uncertain. The changes in RAND-ALL scores and changes in asthma symptoms scores or PEFs were not parallel.

Table 8.4.4.4.6. Mean Changes From Baseline (Last Double-Blind Observation) to the Last Observation in the RAND-ALL Child Health Status Score. [110:109]

Variable	Open-Label Treatment	
	Conventional Asthma Therapy	Budesonide Nebulizing Suspension
Mean Change from Baseline		
RAND-ALL Score	1.2	6.7
95% CI	-2.7, 5.1	4.0, 9.4
(n)	(80)	(177)

8.4.4.4.7 *Health Care Utilization*

In general, the health care utilization variables and indirect economic endpoints were not very different between two treatment groups. [110:111]

Reviewer's Comments: The proportion of patients who had unscheduled doctor visits, emergency room visits or hospitalizations was slightly higher in the budesonide group compared to the conventional asthma therapy group.

Table 8.4.4.4.7. 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	157	124(79%)
	Conventional	73	61 (84%)
Asthma Related Days Absent From School[1]	Budesonide	157	124 (79%)
	Conventional	73	60 (82%)
Days Routine Interrupted	Budesonide	179	136 (76%)
	Conventional	83	66 (80%)
Unscheduled Doctor Visits	Budesonide	179	143 (80%)
	Conventional	83	61 (73%)
Asthma Related Unscheduled Doctor Visits	Budesonide	179	142 (79%)
	Conventional	83	61 (73%)
Emergency Room Visits	Budesonide	179	63 (35%)
	Conventional	83	24 (29%)
Asthma Related Emergency Room Visits	Budesonide	179	62 (35%)
	Conventional	83	25 (30%)
Hospitalizations	Budesonide	179	29 (16%)
	Conventional	83	9 (11%)

[1] Only those children attending school/play school/daycare were included.
Data Source: [110:111; Section 14.2., Table 8]

8.4.4.5 Safety Analysis

[110:51-66]

8.4.4.5.1 Extent of Exposure

See Section 8.4.4.2.3.

8.4.4.5.2 Adverse Events

[110:51-59]

8.4.4.5.2.1 Brief Summary of Adverse Events

There were no deaths reported during the study.

There were a total of 21 SAEs in 19 patients reported (4 in the conventional asthma therapy group; 17 in budesonide group) (Table 8.4.4.5.2.4). A total of two patients were discontinued from the study due to AEs (one in each group) (Table 8.4.4.5.2.5).

The percentages of reported AEs of severe intensity were similar for both groups (31% of patients in the conventional asthma therapy group; 36% of patients in the budesonide group). [110:153-5] After adjusting for the length of time in the study there were no clinically relevant differences in the frequency of reported AEs.

8.4.4.5.2.2 Display of All Adverse Events

A total of 251 (92%) patients experienced adverse events during the open-label phase, including 170 (93%) in the budesonide group and 81 (90%) in the conventional asthma therapy group.

Table 8.4.4.5.2.2.A. Summary of Reported Adverse Events in the Study 04-3069B (N=272). [134:146]

	Budesonide Nebulizing Suspension (n=182)	Conventional Asthma Therapy (n=90)
No. of Patients with an AE	170 (93%)	81 (90%)
No. of Patients with a Serious AE	15 (8%)	4 (4%)
No. of Patients Who Discontinued from the Study Due to an AE	1 (<1%)	1 (1%)

The frequency of AEs that occurred in ≥3% of the patients randomized to budesonide group and adjusted for length of time in the study is shown in Table 8.4.4.5.2.2.

The most frequently reported AEs included respiratory infection (61%), sinusitis (24%) and fever (23%). After adjusting for the length of time in the study with Proportional Hazards Model, the incidence of reported AEs were similar between treatment groups except for abdominal pain, which was statistically significant higher in the conventional asthma therapy group (relative risk, 2.436).

Reviewer's Comments: The incidence of pneumonia was also higher in the conventional asthma therapy group compared to the budesonide group (relative risk, 2.484). The etiology of these observations, i.e., higher relative risk of abdominal pain and pneumonia in conventional therapy group, was not clear.

Table 8.4.4.5.2.2B. Summary of Most Frequently Reported AEs (≥3% of Patients in the Budesonide Group) That Began During Open-Label Treatment With Relative Risks (From Proportional Hazards Model) and 95% Confidence Limits, and Adjusted for Length of Time (Per 12 Patient-Months) in the Study.

Body System/AE	Incidence of AEs Beginning in Open-Label			Relative Risk	95% Confidence Interval	Frequency per 12 Pt-Months	
	Conv. Asthma Therapy (n=90)	Budesonide Nebulizing Suspension (n=182)	Total			Conv. Asthma Therapy	Budesonide Nebulizing Suspension
Respiratory System Disorders							
Respiratory Infection	49 (54%)	118 (65%)	167 (61%)	0.854	(0.61, 1.19)	0.7	0.7
Sinusitis	19 (21%)	47 (26%)	66 (24%)	0.924	(0.54, 1.57)	0.3	0.3
Rhinitis	9 (10%)	29 (16%)	38 (14%)	0.684	(0.32, 1.44)	0.1	0.2
Pharyngitis	10 (11%)	22 (12%)	32 (12%)	1.111	(0.53, 2.35)	0.1	0.1
Bronchitis	7 (8%)	14 (8%)	21 (8%)	1.221	(0.49, 3.03)	0.1	0.1
Coughing	6 (7%)	12 (7%)	18 (7%)	1.203	(0.45, 3.21)	0.1	0.1
Bronchospasm	6 (7%)	11 (6%)	17 (6%)	1.267	(0.47, 3.42)	0.1	0.1
Pneumonia	9 (10%)	9 (5%)	18 (7%)	2.484	(0.99, 6.26)	0.1	0.1
Body as a Whole							
Fever	17 (19%)	46 (25%)	63 (23%)	0.806	(0.46, 1.41)	0.3	0.3
Accident and/or Injury	11 (12%)	34 (19%)	45 (17%)	0.789	(0.40, 1.56)	0.2	0.2
Flu-Like Disorder	2 (<3%)	8 (4%)	10 (4%)	0.610	(0.13, 2.87)	0.0	0.0
Pain	3 (3%)	5 (3%)	8 3%)	1.374	(0.33, 5.76)	0.0	0.0
Platelet, Bleeding & Clotting Disorders							
Epistaxis	2 (<3%)	5 (3%)	7 (3%)	0.980	(0.19, 5.05)	0.0	0.0

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Body System/AE	Incidence of AEs Beginning in Open-Label			Relative Risk	95% Confidence Interval	Frequency per 12 Pt-Months	
	Conv. Asthma Therapy (n=90)	Budesonide Nebulizing Suspension (n=182)	Total			Conv. Asthma Therapy	Budesonide Nebulizing Suspension
Table G continued from previous page							
Resistance Mechanism Disorders							
Otitis Media	15 (17%)	35 (19%)	50 (18%)	1.022	(0.56, 1.87)	0.2	0.2
Infection Viral	11 (12%)	20 (11%)	31 (11%)	1.365	(0.65, 2.85)	0.2	0.1
Varicella	4 (4%)	9 (5%)	13 (5%)	1.054	(0.32, 3.42)	0.1	0.1
Moniliasis	1 (<3%)	8 (4%)	9 (3%)	0.289	(0.04, 2.32)	0.0	0.0
Gastrointestinal System Disorders							
Gastroenteritis	5 (6%)	22 (12%)	27 (10%)	0.532	(0.20, 1.41)	0.1	0.1
Vomiting	7 (8%)	12 (7%)	19 (7%)	1.396	(0.55, 3.55)	0.1	0.1
Diarrhea	2 (<3%)	12 (7%)	14 (5%)	0.396	(0.09, 1.77)	0.0	0.1
Abdominal Pain	10 (11%)	10 (5%)	20 (7%)	**2.436**	**(1.01, 5.86)**	0.1	0.1
Nausea	3 (3%)	6 (3%)	9 (3%)	1.026	(0.30, 4.83)	0.0	0.0
Pharynx Disorder	0 (0%)	5 (3%)	5 (2%)	-	-	0.0	0.0
Skin & Appendages Disorders							
Rash	6 (7%)	15 (8%)	21 (8%)	0.931	(0.36, 2.40)	0.1	0.1
Urticaria	5 (6%)	6 (3%)	11 (4%)	2.078	(0.63, 6.81)	0.1	0.0
Dermatitis Fungal	0 (0%)	5 (3%)	5 (2%)	-	-	0.0	0.0

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Body System/AE	Incidence of AEs Beginning in Open-Label			Relative Risk	95% Confidence Interval	Frequency per 12 Pt-Months	
	Conv. Asthma Therapy (n=90)	Budesonide Nebulizing Suspension (n=182)	Total			Conv. Asthma Therapy	Budesonide Nebulizing Suspension
Table G continued from previous page							
Central & Peripheral Nervous Sys. Disorder							
Headache	12 (13%)	24 (13%)	36 (13%)	1.139	(0.57, 2.28)	0.2	0.1
Convulsions	1 (<3%)	6 (3%)	7 (3%)	0.390	(0.05, 3.24)	0.0	0.0
Hearing & Vestibular Disorders							
Ear Infection NOS	11 (12%)	26 (14%)	37 (14%)	1.001	(0.49, 2.03)	0.2	0.2
Vision Disorders							
Conjunctivitis	4 (4%)	14 (8%)	18 (7%)	0.665	(0.22, 2.02)	0.1	0.1
Eye Infection NOS	2 (<3%)	5 (3%)	7 (3%)	0.978	(0.19, 5.04)	0.0	0.0

Data source: [110:139-46; Section 14.3.1, Tables 5 and 6]

8.4.4.5.2.3 Analysis of Adverse Events

In all body systems, the incidence of AEs considered by the investigator to be possibly or probably related to treatment was higher in the budesonide group (n=18, 10%) compared to the conventional asthma therapy group (n=2, 2%). Moniliasis was reported in seven (4%) of the patients on budesonide, with no occurrence in the conventional asthma therapy treatment group. The frequency of all the other AEs possibly or probably related to treatment was ≤ 1% in both groups.
[110:147-8]

8.4.4.5.2.4 Serious Adverse Events

There were no deaths reported during this study. A total of 21 SAEs in 19 patients were reported (4 in the conventional asthma therapy group; 17 in the budesonide group). In each case the investigator judged the SAE to be unlikely to be related to study treatment, and all the events resolved without sequelae.

Table 8.4.4.5.2.4. Summary of Serious Adverse Events.[1] [110:57]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Budesonide Nebulizing Suspension:		
01-0131	Bronchospasm/completely recovered.	Unlikely
03-0389	Convulsions/completely recovered.	Unlikely
05-0256	Convulsions/completely recovered.	Unlikely
	Meningitis/completely recovered.	Unlikely
11-0174	Bronchospasm/completely recovered.	Unlikely
12-0185	Sinusitis/completely recovered.	Unlikely
12-0566	Bronchospasm/completely recovered.	Unlikely
13-0366	Pharynx Disorder/completely recovered.	Unlikely
16-0206	Tongue Disorder/completely recovered.	Unlikely
18-0326	Bronchospasm/completely recovered.	Unlikely
18-0328	Bronchospasm/completely recovered.	Unlikely
22-0444	Bronchospasm/completely recovered.	Unlikely
22-0447	Pneumonia Lobar/completely recovered.	Unlikely
	Pneumonia/completely recovered.	Unlikely
22-0452	Accident and/or Injury/completely recovered.	Unlikely
23-0214	Bronchospasm /completely recovered.	Unlikely
28-0505	Fracture/completely recovered.	Unlikely
Conventional Asthma Therapy:		
05-0551	Bronchospasm/completely recovered.	Unlikely
13-0360	Renal Pain/completely recovered.	Unlikely
16-0202	Convulsions/completely recovered.	Unlikely
25-0285	Weight Decrease/completely recovered.	Unlikely

[1] Data sources: [110:151-2, 170-81; and Section 14.3.2, Table and Sections 14.3.3.1, 14.3.3.2]
[2] WHO preferred term.

8.4.4.5.2.5 Discontinuations Due to Adverse Events

A total of two patients were discontinued from the study due to AEs (one in each treatment group). One of the patients (Patient 07-0135; randomized to budesonide) had an increase in SGPT which was not recovered at the final study visit (130 U/L). The patient was referred to his primary care physician. The investigator was unable to obtain follow-up information on this patient.

Table 8.4.4.5.2.5. Summary of Discontinuations due to Adverse Events.[1] [110:58]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Budesonide Nebulizing Suspension:		
07-0135	SGPT Increased/Patient was referred to his primary care physician; follow-up information on patient's recovery is unavailable.	Unlikely
Conventional Asthma Therapy:		
27-0543	Bronchitis/completely recovered.	Unlikely

[1] Data sources: [110:181; Sections 14.3.3.2]
[2] WHO preferred term.

8.4.4.5.2.6 Adverse Events of Severe Intensity

[110:153-67]

In all body systems, the incidence of severe AEs was higher in the budesonide group (n=66, 36%) compared to the conventional asthma therapy group (n=28, 31%). Respiratory infection was most frequently reported with incidences of 10% in the conventional asthma therapy group compared to 15% in the budesonide group. Bronchospasm occurred in 3% of the patients on conventional asthma therapy compared to 6% of the patients on budesonide. Viral infections were reported in 6% of the patients on conventional asthma therapy compared to 2% patients on budesonide. All other severe AEs were reported with incidences of ≤4% in any treatment group.

Three of the severe AEs were judged by the investigators to be possibly causally-related to budesonide: one headache, one coughing, and one bronchospasm. All three patients recovered completely.

8.4.4.5.3 Assessment of HPA-Axis

[110:61-3]

Data from Clinical Center #17 were excluded due to problems with cortisol testing at that center. All of the patients in the conventional asthma therapy group assessed showed normal responsiveness in cortisol levels after stimulation with ACTH at Week 52. In contrast, in the budesonide group, 14% of patients who had normal responsiveness in ACTH-stimulated cortisol levels at baseline showed an abnormal responsiveness at Week 52.

Reviewer's Comments:1. Of note, there was a decrease (-22.3 nmol/L) in the adjusted mean change in ACTH-stimulated cortisol levels from baseline in the budesonide group and an increase (39.1 nmol/L) in the conventional asthma therapy group. The clinical significance of this

observation is uncertain but does suggest a measurable systemic effect of nebulized budesonide. 2. The mean baseline cortisol level of the conventional asthma therapy group (249 nmol/L) was lower than that of the budesonide group (320 nmol/L).

Table 8.4.4.5.3.A. Summary Results of ACTH-Stimulated Cortisol Tests for Patients Who Completed One Year of Open-Label Treatment (Excluding Data From Center #17).[1]

Variable		Open-Label Treatment	
		Conventional Asthma Therapy	**Budesonide Nebulizing Suspension**
Cortisol Levels (nmol/L)			
All patients:			
Basal:	Baseline	249	320
	Week 52	304	301
		(n=16)	(n=41)
ACTH Stimulated:	Baseline	690	691
	Week 52	725	651
		(n=14)	(n=40)
Male Patients:			
Basal:	Baseline	228	333
	Week 52	274	318
		(n=8)	(n=32)
ACTH Stimulated:	Baseline	659	693
	Week 52	681	664
		(n=7)	(n=30)
Female Patients:			
Basal:	Baseline	271	272
	Week 52	334	238
		(n=8)	(n=9)
ACTH Stimulated:	Baseline	721	684
	Week 52	768	613
		(n=7)	(n=10)
Adjusted Mean Changes in ACTH-Stimulated Cortisol Levels from Baseline[2] (p-value vs. conventional asthma therapy)			
All Patients		39.1	-22.3 (p=0.293)
Male Patients		87.1	-9.1 (p=0.284)
Female Patients		3.1	-70.6 (p=0.356)

[1] Data source: [110:228; Section 14.3.5, Table 4b]
[2] Means adjusted for Center Effect.

Table 8.4.4.5.3.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 (Excluding Data From Center 17).[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%)	3 (100%)	2 (50%)	2 (50%)
	Normal	0 (0%)	11 (100%)	5 (14%)	31 (86%)
Male Patients	Abnormal	0 (0%)	1 (100%)	2 (67%)	1 (33%)
	Normal	0 (0%)	6 (100%)	3 (11%)	24 (89%)
Female Patients	Abnormal	0 (0%)	2 (100%)	0 (0%)	1 (100%)
	Normal	0 (0%)	5 (100%)	2 (23%)	7 (77%)

[1] Data source: [110:229; Table 5 of Section 14.3.5]

[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.

8.4.4.5.4 *Evaluation of Clinical Laboratory Tests*

Overall, the number of clinically significant laboratory test value abnormalities was low, all abnormal values occurred at an incidence of ≤2%, and many were present at baseline. With the exception of alkaline phosphatase, there were no apparent differences between the means at baseline and the last visit for any laboratory test variable in either group and the mean changes from the baseline values for any laboratory test variable were similar in both groups. For alkaline phosphatase, the mean change from the baseline to the last visit was -26.5±256.0 (range -3188.0, 97.0) in the budesonide group, compared to 7.7±41.3 (range -76.0, 190.0) in the **conventional asthma therapy group**. This large difference was most likely due to a patient (Patient 05-0549; randomized to budesonide) who had an abnormally high re-test value at randomization possibly due to a viral infection. The majority of clinically significant values were judged by the investigator to be unrelated to study treatment and due to concomitant diseases such as viral infections or allergic rhinitis. In a few cases an explanation could not be found.
[110:183-201]

8.4.4.5.5 *Vital Signs and Physical Findings*

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 examination findings during treatment between two treatment groups. The most frequently observed physical examination

abnormalities were in the respiratory system, with nasal and sinus discharge being the most frequent. [110:215-226]

8.4.4.5.6 *Assessment Of Oral And Nasal Fungal Cultures*

There were no apparent differences between treatment groups in changes in oral cavity fungal cultures from the baseline to Week 52. While the incidence of clinically significant abnormalities in oral cavity fungal cultures in the conventional asthma therapy group (2%) was lower than that of the budesonide groups (5%). [110:234-6]

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

[110:63-6, 237-49]

Either as a whole group or stratified by gender, the mean measured growth velocity (cm/year) of patients on budesonide was numerically smaller than that of patients on conventional asthma therapy (0.84, 0.9, and 0.65 cm/year for all patients, male patients, and female patients, respectively).

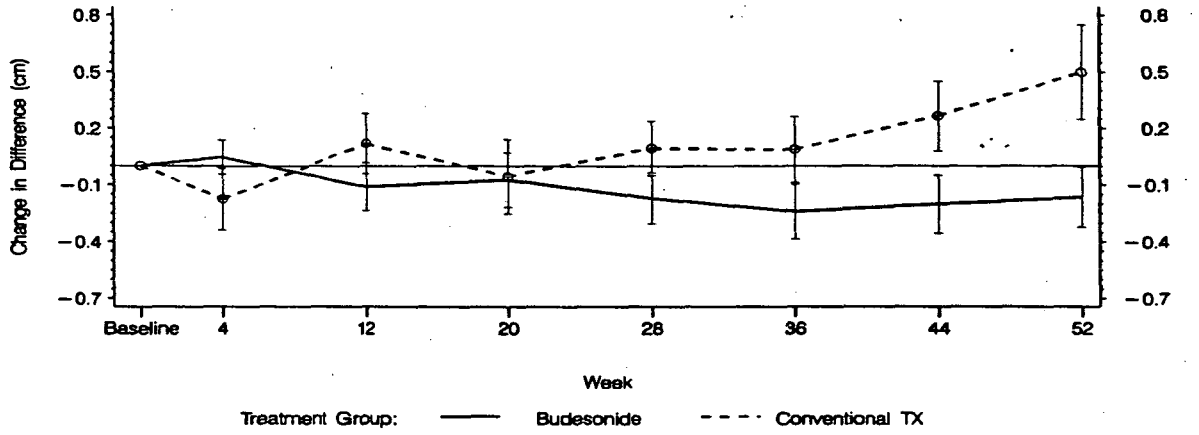
Reviewer's Comments: The difference in the mean measured growth velocity was statistically different between the budesonide and conventional asthma therapy groups, the magnitude of growth retardation in the budesonide group (0.84 cm/year) was similar to that observed in other studies using intranasal or oral inhaled steroids (≈ 0.8-1.0 cm/year). See Sections 2.3.2-3 of Statistical Review for details.

Table 8.4.4.5.7A. 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. [110:66]

Stratification Group	Treatment Group	n	Mean Measured Growth Velocity
All Patients	Budesonide	150	6.55±2.08
	Conventional	58	7.39±2.51
Male Patients	Budesonide	103	6.38±1.89
	Conventional	36	7.28±2.64
Female Patients	Budesonide	47	6.91±2.43
	Conventional	22	7.56±2.33

The mean (± standard error) 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 also demonstrated a similar result (Figure 8.4.4.5.7). [110:65, 259]

Figure 8.4.4.5.7. 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. [110:65]



There were no apparent differences between two treatment groups in the proportion of patients showing a shift in observed height relative to standard 50th percentile height from baseline to Week 52 (Table 8.4.4.5.7.B).

Table 8.4.4.5.7B. 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. [110:246]

Parameter	Baseline	Week 52			
		Conventional Asthma Therapy		Budesonide Nebulizing Suspension	
		Below	Above	Below	Above
Observed Height[1]	Below	23	2	66	4
	Above	5	28	11	72

[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: [110: 246; Section 14.3.5, Table 21]

8.4.5 Conclusions and Comments of Study Results

This was a randomized, active-controlled, one-year, open-label extension of a previous 12-week, double-blind, placebo-controlled study (Study 04-3069) to evaluate the safety and efficacy of budesonide nebulizing suspension ranging from 0.25 mg QOD to 1.0 mg QD in asthmatic infants and young children.

The results demonstrated that budesonide numerically improved most of efficacy variables compared to the conventional asthma therapy group, which included the following: the proportion of patients who discontinued from the study (statistically significant), the improvements in asthma symptom scores and lung function (morning PEF, FEV_1, FVC and corresponding $FEF_{25-75\%}$), and the proportion of patients requiring oral prednisone for asthma deterioration (Table 8.4.5).

Unexpectedly, the reduction in breakthrough medication use was greater for the conventional asthma therapy group than for the budesonide group. The etiology of this observation was not clear. 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. One possibility is that patients in the conventional asthma therapy group used albuterol more than the maintenance dose and did not record this as use of breakthrough medication.

The safety evaluations did not reveal apparent difference between two treatment groups in reported adverse events or regular clinical laboratory tests. After adjusting for length of time in the study, there were no obvious differences in the type, incidence, or severity of AEs between treatment groups. There was a numerical increase in the incidence of clinically significant abnormalities in oral cavity fungal cultures in the budesonide groups (5%) compared to the conventional asthma therapy group (2%). Of note, there was a decrease in the adjusted mean change in ACTH-stimulated cortisol levels from baseline in the budesonide group (-22.3 nmol/L) compared to the conventional asthma therapy group (39.1 nmol/L). In the budesonide group, 14% of patients who had normal responsiveness in ACTH-stimulated cortisol levels at baseline showed abnormal responsiveness at Week 52 as compared to 0% in the conventional asthma therapy group.

Importantly, the growth velocity (cm/year) was significantly reduced in the budesonide group compared to the conventional asthma therapy group. The magnitude of growth retardation in the budesonide group (0.84 cm/year) was similar to that observed in other studies using intranasal or oral inhaled steroids ($\approx$ 0.8-1.0 cm/year).

Table 8.4.5. Mean changes from baseline in efficacy variables[1].

Mean Change from Baseline (Week 0-52)[2]	Open-Label Treatment: Conventional Asthma Therapy	Open-Label Treatment: Budesonide Nebulizing Suspension
Asthma Symptom Score:		
Nighttime	-0.05	-0.09
95% CI	-0.18, 0.09	-0.19, 0.01
Daytime	-0.09	-0.10
95% CI	-0.23, 0.05	-0.20, 0.00
Use of Breakthrough Medication:		
Days	-3.4	-1.5
95% CI	-4.6, -2.3	-2.3, -0.7
Nebulizations (of Nebulizer)/day	-0.21	-0.06
95% CI	-0.5, 0.1	-0.2, 0.1
Puffs (of pMDI)/day	-0.40	0.09
95% CI	-1.5, 0.7	-0.8, 1.0
PEF (L/min)[2]:		
Morning	5.9	7.2
95% CI	-8.4, 20.3	-4.0, 18.4
Evening	6.1	5.9
95% CI	-8.9, 21.2	-5.8, 17.6
Spirometry[2]:		
FEV_1 (L/min)	0.05	0.12
95% CI	-0.08, 0.18	0.03, 0.21
FVC (L/min)	0.09	0.14
95% CI	-0.08, 0.26	0.03, 0.25
$FEF_{25-75\%}$	0.05	0.15
95% CI	-0.12, 0.21	0.04, 0.26
Proportion of Patients Discontinued (%) (p-value vs. conventional therapy)	32	14 (0.001)*
Prednisone Use:		
Number (%) of Patients that Used Oral Prednisone During the Study:		
No	42 (47%)	98 (54%)
Yes	48 (53%)	84 (46%)
Average Total Daily Amount Used (mg):		
Mean±SD	0.53±0.70	0.47±0.96

[1] Data sources: Tables 8.4.4.1B, 8.2.4.4.1.1-6.
[2] For those patients who were able to perform the test.

8.5 Non-U.S. Supportive Studies

8.5.1 Study 04-2213: Budesonide Suspension for Nebulization in Infants with Asthma.

8.5.1.1 Objectives

[76:33]

To determine whether budesonide nebulizing suspension could replace oral prednisolone treatment (single-dose, alternate morning) in the prophylaxis of steroid-dependent severe asthma in preschool children.

8.5.1.1.1 Efficacy Variables

[76:3, 40-1]

- Dose of prednisolone taken.
- Nighttime and daytime asthma symptoms (0-3 scale).
- Use of nebulized bronchodilator (terbutaline) as breakthrough medication.
- Dose of theophylline taken.
- A visual analogue scale (0-10 cm) recording by parents during each clinical visit to assess the health status of the child during the week prior to the clinical visit.
- Physician's assessment of the child's health status during clinic visits.

8.5.1.1.2 Safety Variables

[76:3, 41-2]

- Reported adverse events.
- Throat swabs for *candida albicans*.

8.5.1.2 Design

[76:33-40]

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted in three study centers in Israel, Denmark and England.

After a run-in period of two to four weeks, the eligible children were randomized to either 1.0 mg BID budesonide nebulizing suspension or nebulized placebo for eight weeks. Study drug was delivered via a [redacted] nebulizer with a face mask or a mouthpiece, connected to a [redacted] compressor. During each week of the double-blind treatment period, parents were instructed to reduce their child's oral prednisolone dose by 25-33% of the initial dose provided that the child was symptom-free during the previous week, or had fewer symptoms than in the previous week and did not require an inhaled bronchodilator (terbutaline) more than once a day during the preceding week.

The double-blind treatment period was followed by an 8-week open-label period during which children that had been randomized to the placebo group were further treated with 1.0 mg BID budesonide nebulizing suspension provided that they were still on oral prednisolone at the end of the double-blind period. In the open-label period, the children

who had been treated with budesonide nebulizing suspension 1.0 mg BID were treated with budesonide nebulizing suspension 0.5-1 mg BID.

8.5.1.3 Study Population

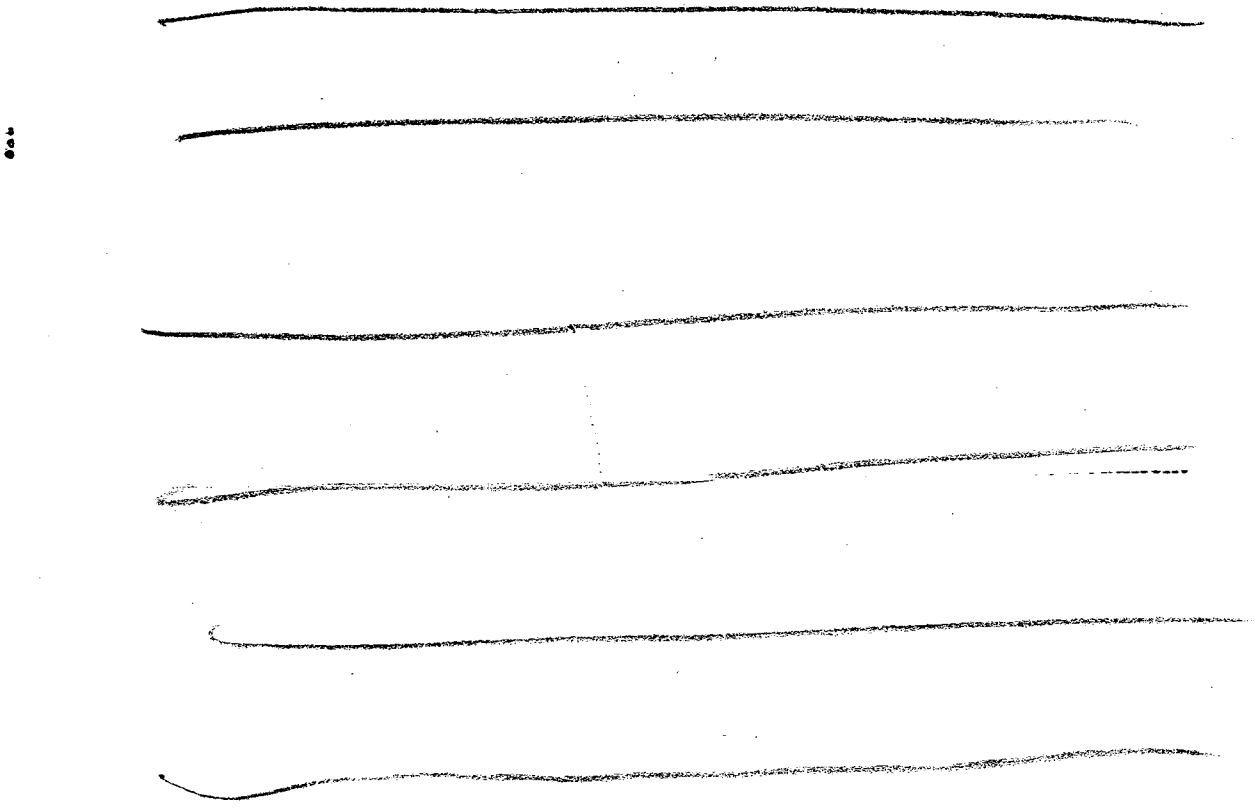
[76:2, 44]

- Thirty-seven infants and children were randomized into the study, of whom 36 (24 males and 12 females) were evaluable for efficacy (one placebo patient did not take any study medication).
- The children were oral steroid-dependent asthmatics between the ages of 9-60 months (mean age of 26.7±13 months) with a mean duration of asthma of 3-42 months (mean duration of asthma of 17.5±8.7 months).
- Prior to the start of the study, all children were treated with oral steroids on alternate days (mean dose of 1.3± 0.5 mg/kg body weight; range 0.78-3.57 mg/kg).
- The first patient was enrolled into the study in January, 1988. The last patient completed the study in April, 1989.

8.5.1.4 Results

8.5.1.4.1 Efficacy

[76:46-61]



8.5.1.4.2 Safety

[76:4, 6-10]

There were no deaths reported during the study. There were 11 discontinuations, 9 in the placebo group and 2 in the budesonide nebulizing suspension group. Among these, 6 were due to asthma deterioration. A total of 14 SAEs in 10 patients were reported. All of the SAEs except one (respiratory infection) were due to asthma deterioration. All but one asthma deterioration (that could not be classified) were classified as unlikely related to budesonide nebulizing suspension by the investigators. The most frequently reported AEs (≥ 2 of patients in the budesonide nebulizing suspension group) during the treatment period are shown in the following table. All but one (ear infection NOS) occurred more frequently with budesonide nebulizing suspension than placebo during the double-blind treatment period.

Table 8.5.1.4.2. Summary of Most Frequently Reported AEs (≥ 2 of Patients in the Budesonide or Placebo Group) during the Treatment Period.

Body System/AE	Placebo		Budesonide Nebulizing Suspension	
	Run-in Period (n=19)	Treatment Period (n=19)	Run-in Period (n=17)	Treatment Period (n=18)
Respiratory System Disorders				
Respiratory Infection	2 (11%)	4 (21%)	2 (12%)	7 (39%)
Rhinitis	1 (5%)	2 (11%)	1 (6%)	4 (22%)
Asthma Aggravated	0 (0%)	3 (16%)	0 (0%)	3 (17%)
Body as a Whole				
Fever	1 (5%)	2 (11%)	3 (18%)	3 (17%)
Malaise	0 (0%)	0 (0%)	0 (0%)	2 (11%)
Resistance Mechanism Disorders				
Infection	1 (5%)	3 (16%)	3 (18%)	4 (22%)
Moniliasis	0 (0%)	0 (0%)	2 (12%)	4 (22%)
Hearing & Vestibular Disorders				
Ear Infection NOS	2 (11%)	2 (11%)	0 (0%)	2 (11%)

Data source: [76:17-8]
NOS: Not otherwise specified.

Reviewer's Comments: During the treatment period, the increased incidences of moniliasis, malaise, respiratory infection, and rhinitis in the budesonide nebulizing suspension group, compared to the placebo group, were possibly treatment related.

8.5.2 *Study 04-2188: Budesonide Suspension for Nebulization in Children with Asthma.*

8.5.2.1 Objectives

[88:27]
To evaluate the safety and efficacy as well as the dose-response relationship of three doses of budesonide nebulizing suspension in asthmatic children.

8.5.2.1.1 Efficacy Variables

[88:1, 35-6]
Physician's Recordings:

- Pre- and post-exercise (6 minute cycling with load regulation) spirometry (FEV_1, FVC, $FEF_{25-75\%}$, and PEF).

Diary Variables:

- Morning and evening PEFs.
- Daytime asthma symptom scores (0-6 scale).
- Nighttime asthma symptom scores (0-4 scale).
- Use of β_2-agonist.