treatment groups were similar with respect to general physical condition.

The treatment groups were similar with respect to diagnoses present at baseline. Approximately half of the patients had allergic rhinitis. Dermatitis, otitis media, chronic rhinitis, chronic sinusitis, and headache were represented in 7-11% of patients. Other concomitant diseases were present in 6% or fewer of the patients. The most frequently reported past diagnosis was otitis media (39%).

8.2.4.2.3 Prior and Concomitant Medications

[38:85-6]

8.2.4.2.3.1 Asthma Medications

Prior asthma medications: The treatment groups were similar with respect to the prior use of asthma drugs. All of the patients randomized had used asthma medications before enrollment in the study. The asthma medications most used frequently prior to the study were albuterol (oral and/or inhaled salbutamol; >99%), cromoglicic acid (cromolyn sodium; 76%), prednisolone (19%); beclomethasone (8%) and theophylline (7%). [38:138-9]

Concomitant asthma medications: The use of β_2-agonists predominated, with 99% of patients receiving oral and/or inhaled albuterol at some time during the treatment phase. Approximately 17% of the patients received parenteral/oral steroids at some time during the study, and about 11% received other anti-inflammatory agents. [38:140-1]

8.2.4.2.3.2 Non-Asthma Medications

Prior non-asthma medications: The prior use of non-asthma medications was similar among treatment groups. Drug classes mentioned most frequently were dermatologic preparations (64%), nasal preparations (41%), systemic antibacterials (29%), analgesics (26%), antihistamines (16%), cough and cold preparations (12%), and corticosteroid dermatologics (8%). [38:142-6]

Concomitant non-asthma medications: The use of concomitant non-asthma medications was similar among treatment groups. Drug classes mentioned most frequently were dermatologic preparations (60%), analgesics (50%), systemic antibacterials (48%), nasal preparations (46%), antihistamines (21%), cough and cold preparations (19%), and anti-inflammatory and antirheumatic products (9%). [38:147-53]

8.2.4.3 Measurements of Treatment Compliance

[38:86; 42:10]

In all treatment groups, the proportion of patients who achieved at least 80% compliance with respect to the administration of study treatments was in the range of 95-99% for Week 2; 89-96% for Week 4; 82-96% for Week 8; and 74-87% for Week 12. Compliance with respect to the study procedures was in the range of 84-95% for Week 2; 82-99% for Week 4; 76-87% for Week 8; and 68-82% for Week 12.

8.2.4.4 Efficacy Analysis

8.2.4.4.1 Primary Efficacy Variables

[38:87-92]

8.2.4.4.1.1 Asthma Symptom Scores; All Patients Treated, Last Value Carried Forward, Total Population

Table 8.2.4.4.1.1. Asthma symptom scores; All Patients Treated, Last Value Carried Forward, Total Population. [38:87]

Variable (Weeks 0-12)		Placebo	Budesonide Nebulizing Suspension, QD		
			0.25 mg	0.5 mg	1.0 mg
Asthma Symptom Score (scale of 0-3):[1]	n	92	91	82	93
Mean Change from Baseline[2]					
Nighttime		-0.16	-0.49	-0.42	-0.42
(p-value vs. placebo)			(0.001)**	(0.010)**	(0.009)*
Daytime		-0.26	-0.57	-0.46	-0.50
(p-value vs. placebo)			(0.002)**	(0.049)*	(0.016)*

[1] Data sources: [38:155-8; Section 14.2, Table 1]
[2] Mean change adjusted for center effect.
* 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.

For nighttime asthma symptom scores, the adjusted mean changes from baseline to Weeks 0-12 in patients of the three budesonide groups were statistically significantly greater compared to placebo ($p \leq 0.010$). When the Dunnett's adjustment was applied, the 0.25 mg QD and 0.5 mg QD budesonide groups maintained their superiority over the placebo group. This is shown graphically in Figure 8.2.4.4.1.1A.

For daytime asthma symptom scores, the adjusted mean changes from baseline to Weeks 0-12 in patients of the three budesonide groups were statistically significantly greater compared to placebo ($p \leq 0.049$). When the Dunnett's adjustment was applied, only the 0.25 mg QD budesonide group maintained superiority over the placebo group. This is shown graphically in Figure 8.2.4.4.1.1B.

Reviewer's Comments: The improvements in asthma symptom scores were not dose-dependent.

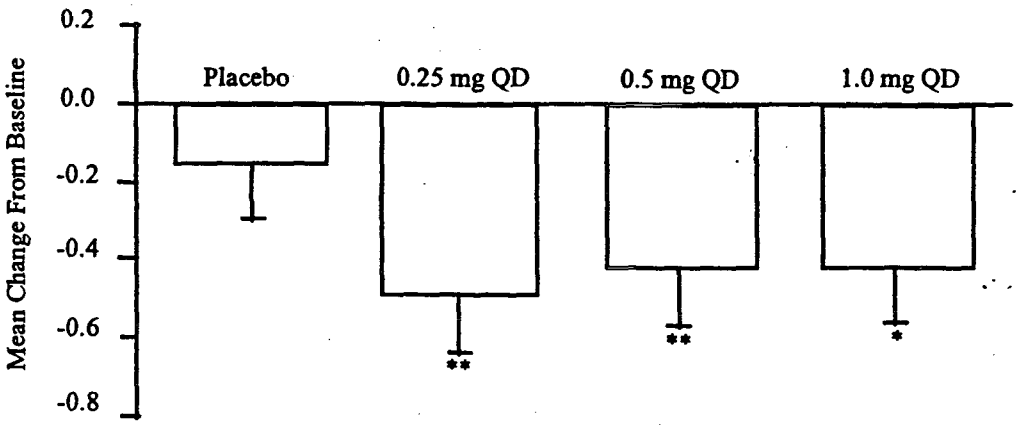
Compared to the placebo group, the onset of numerical improvement in nighttime and daytime asthma symptom scores of each budesonide group was observed by Week 2 and was sustained throughout the 12-week treatment phase. This is shown graphically in Figure 8.2.4.4.1.1C and D.

Reviewer's Comments: However, when comparing each individual budesonide group to placebo, the statistically significant differences for either nighttime or daytime symptom scores in all three budesonide group were not observed until Weeks 4-6. [38:155, 157]

> If the time to onset responses is defined as the first day associated with a statistically significant difference in changes from the baseline of asthma symptom scores between the budesonide and placebo treatment groups, statistically significant differences for nighttime asthma symptom scores between all budesonide groups combined compared to placebo were observed on Day 4 ($p<0.050$) and that for daytime asthma symptom scores on Day 2 ($p<0.050$). [Amendment 1/7/98]

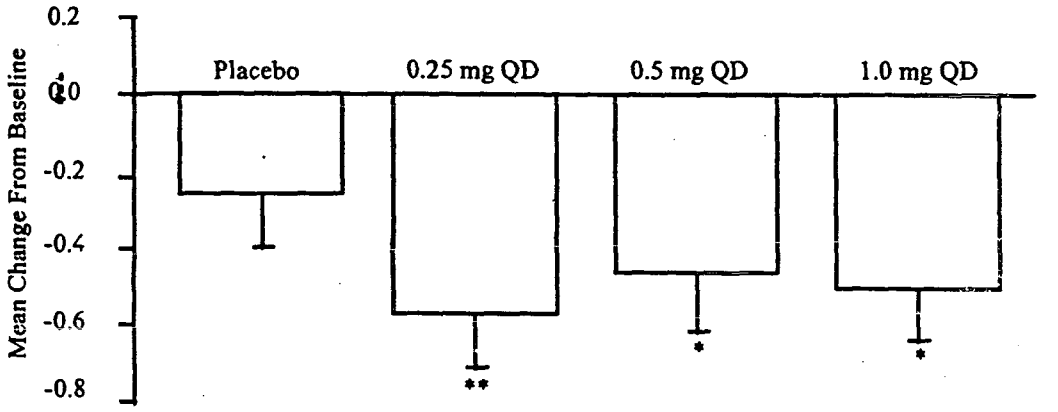
Reviewer's Comments: While the above separations from placebo were observed, the differences in changes of daytime asthma symptom scores between the budesonide and placebo groups were not statistically significant in most of the first 14 days of treatment phase (except Days 2-3, 5-6, and 8-9). In contrast, the significant differences in changes of nighttime asthma symptom scores were maintained in most of the first 14 days (except Day 14).

Figure 8.2.4.4.1.1A. Mean change[1] from baseline to double-blind treatment (Weeks 0-12) in nighttime asthma symptom scores ±95% C.I.; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [38:89]



[1] Means adjusted for center effect.
* p≤0.05 versus placebo level before Dunnett's adjustment.
** p≤0.05 versus placebo level before and after Dunnett's adjustment.

Figure 8.2.4.4.1.1B. Mean change[1] from baseline to double-blind treatment (Weeks 0-12) in daytime asthma symptom scores ±95% C.I.; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [38:89]



[1] Means adjusted for center effect.
* p≤0.05 versus placebo level before Dunnett's adjustment.
** p≤0.05 versus placebo level before and after Dunnett's adjustment.

Figure 8.2.4.4.1.1C. Summary of mean nighttime asthma symptom scores; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [38:90]

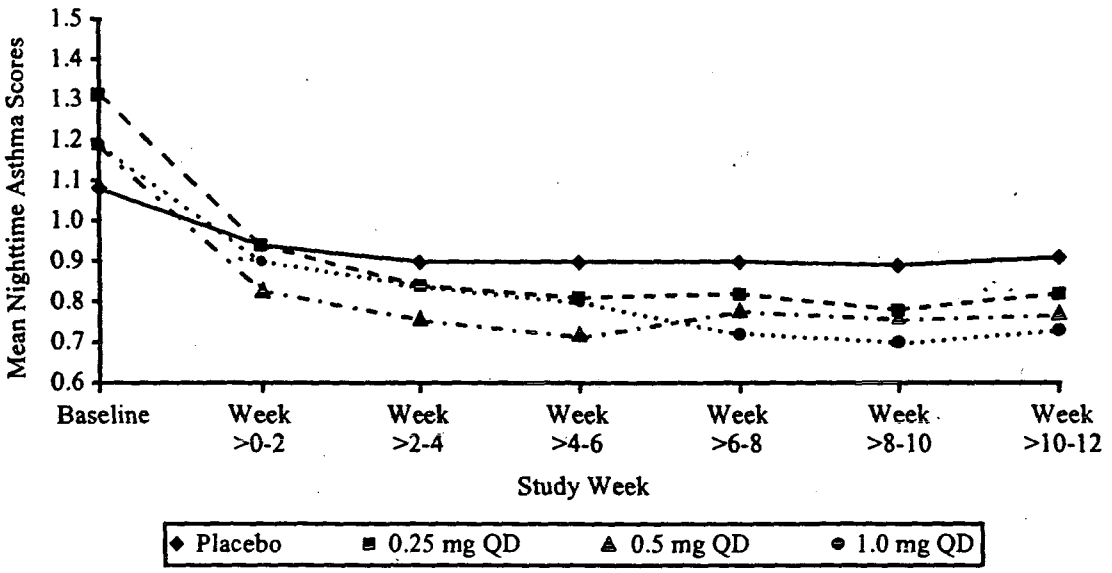
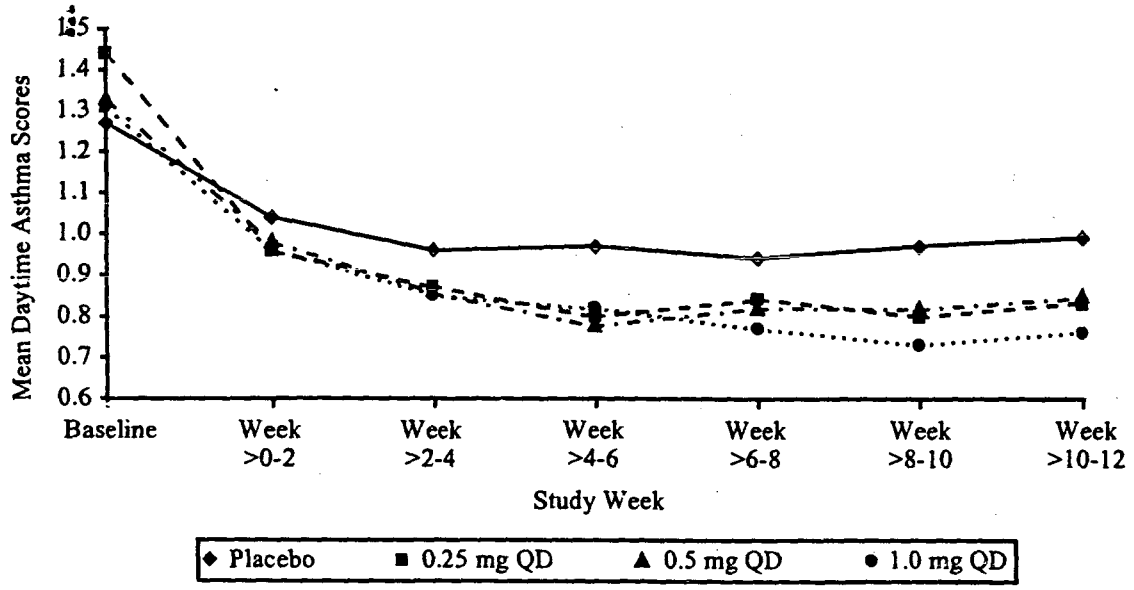


Figure 8.2.4.4.1.1D. Summary of mean daytime asthma symptom scores; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [38:90]



8.2.4.4.1.2 Nighttime and Daytime Asthma Symptom Scores, by Prior Cromolyn Sodium (Intal®) Therapy; All Patients Treated, Last Value Carried Forward

Of each treatment group, there were no apparent differences in asthma symptom scores from baseline to double-blind treatment phase between patients who had been taking cromolyn sodium and those not taking cromolyn sodium prior to enrollment in the study. [38:176-7]

8.2.4.4.1.3 Nighttime and Daytime Asthma Symptom Scores, by Baseline Symptom Severity Score; All Patients Treated, Last Value Carried Forward

In all treatment groups (including placebo), the patients whose symptoms were most severe at baseline showed a higher degree of improvement than those who were judged mild or moderate at baseline. [38:178-9]

8.2.4.4.1.4 Nighttime and Daytime Asthma Symptom Scores, by Age Classification; All Patients Treated, Last Value Carried Forward

For patients who were 4 year-old or younger in comparison to those older than 4 year-old, there were no apparent differences in asthma symptom scores in any of the treatment groups. [38:176-7]

8.2.4.4.1.5 Nighttime and Daytime Asthma Symptom Scores, Summary of Changes (Improved; No Change; Worse), Baseline to Double-Blind Treatment Phase; All patients Treated, Last Value Carried Forward

For both nighttime and daytime asthma symptom scores, the proportion of patients classified as improved by at least 0.5 points in the budesonide groups was higher compared to the placebo group. [38:181-2]

For nighttime symptom sores, 40-51% of the patients treated with budesonide were classified as having improved by at least 0.5 points compared to 28% for placebo. Four to 6% of the patients on budesonide were classified as having worsened by at least 0.5 points compared to 7% for placebo. Forty-five to 55% of the patients on budesonide were classified as having no change (-0.5 points < change < 0.5 points) compared to 65% for placebo.

For daytime asthma symptom scores, 47 to 55% of the patients treated with budesonide showed improvement by at least 0.5 points compared to 37% for placebo. Five percent of the patients in any treatment group were classified as worsened by at least 0.5 points. Forty to 47% of the patients on budesonide were classified as having no change (-0.5 points < change < 0.5 points) compared to 58% for placebo.

Reviewer's Comments: Altogether, more than half of patients on budesonide were classified as having no change or having worsened in asthma symptom scores (56% for nighttime scores and 49% for daytime scores).

8.2.4.4.1.6 Nighttime and Daytime Asthma Symptom Scores; All Patients Treated, Observed Cases, or Per Protocol (Excluding All Patients with Major Violations of the Protocol)

The results of these analyses were similar to that of the APT, LVCF analysis. [38:174-5]

Reviewer's Comments: However, the adjusted mean change from baseline to Weeks 0-12 for daytime asthma symptom scores of patients in the 0.5 mg QD budesonide group was not significantly different from that of placebo.

8.2.4.4.2 Secondary Efficacy Variables

[38:92-6]

8.2.4.4.2.1 Use of Breakthrough Medication; All Patients Treated, Last Value Carried Forward, Total Population

Patients on budesonide showed reduced use of breakthrough medication from baseline to the treatment phase compared to placebo. The differences between each budesonide regimen and placebo were statistically significant ($p \leq 0.038$).

Table 8.2.4.4.2.1A. Use of breakthrough medication, mean changes from baseline in the number of days patients took breakthrough medication; All Patients Treated, Last Value Carried Forward, Total Population. [38:93]

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension, QD		
		0.25 mg	0.5 mg	1.0 mg
Use of Breakthrough Medicine[1]				
n	92	91	82	93
Baseline	10.8	11.6	11.3	10.6
Mean Change from Baseline[2]	-4.19	-6.26	-6.31	-5.98
(p-value vs. Placebo)		(0.017)*	(0.018)*	(0.038)*

[1] Data source: [38:184; Section 14.2, Table 15]
[2] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

Patients on budesonide showed reduced use of breakthrough medication (as the number of puffs or nebulizations used per day) from baseline to the treatment phase compared to placebo.

Table 8.2.4.4.2.1B. Amount of breakthrough medication used; All Patients Treated, Last Value Carried Forward, Total Population. [38:185]

Variable (Weeks 1-12)	Placebo	Budesonide Nebulizing Suspension, QD		
		0.25 mg QD	0.5 mg BID	1.0 mg QD
Use of nebulizer				
n	51	60	57	57
Baseline[1]	1.55	2.02	1.74	1.88
Mean Change from Baseline[1]	-0.45	-0.92	-0.69	-1.05
Use of pMDI				
n	26	16	14	25
Baseline[1]	2.96	2.90	2.98	2.34
Mean Change from Baseline[1]	-0.32	-0.66	-1.79	-1.22

[1] The number of puffs (* doses) or nebulizations of breakthrough medication used per day; not adjusted for center effect.

Reviewer's Comments: The reduction in use of breakthrough medication (days, puffs of pMDI/day, or nebulizations/day) was not dose dependent.

8.2.4.4.2.2 Proportion of Patient Discontinuations from the Study

See Section 8.2.4.1.

8.2.4.4.2.3 Morning and Evening PEFs; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that Could Perform The Maneuver

There were no statistically significant improvements in the morning or evening PEF in any budesonide group compared to placebo. There were numerical improvements in 0.25 mg QD and 1.0 mg QD budesonide groups compared to placebo.

Table 8.2.4.4.2.3. Mean changes from baseline in morning PEF; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that could perform the maneuvers. [38:203, 208]

Variable (Weeks 0-12)		Placebo	Budesonide Nebulizing Suspension, QD		
			0.25 mg	0.5 mg	1.0 mg
Morning PEF:[1]	n	55	44	41	55
Mean Change from Baseline (L/min)[2] (p-value vs. placebo)		7.1	14.4 (0.135)	6.5 (0.901)	10.9 (0.417)
Evening PEF:[1]	n	55	42	41	54
Mean Change from Baseline (L/min)[2] (p-value vs. placebo)		3.6	11.2 (0.114)	3.8 (0.977)	9.9 (0.169)

[1] For those patients who were able to use a peak flow meter.
[2] Mean change adjusted for center effect.

Reviewer's Comments: The numerical improvement in morning or evening PEF was not dose dependent.

8.2.4.4.2.4 FEV_1, FVC and Corresponding $FEF_{25-75\%}$; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that Could Perform The Maneuvers

Except FEV_1 and FVC for the 0.5 mg BID budesonide group and FEV_1 for the 1.0 mg QD group, there were no significant differences in the mean changes from baseline in FEV_1, FVC or $FEF_{25-75\%}$ between each budesonide group and placebo.

Table 8.2.4.4.2.4. Mean changes from baseline in FEV_1, FVC and Corresponding $FEF_{25-75\%}$; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that could perform the maneuvers. [38:208]

Variable (Weeks 0-12)		Placebo	Budesonide Nebulizing Suspension, QD		
			0.25 mg	0.5 mg	1.0 mg
Spirometry[1]:	n	38	29	28	33
Mean Change from Baseline [2]					
FEV_1 (L)		-0.07	-0.01	0.03	0.03
(p-value vs. placebo)			(0.216)	(0.044)*	(0.033)*
FVC (L)		-0.04	0.05	0.06	0.04
(p-value vs. placebo)			(0.060)	(0.038)*	(0.094)
$FEF_{25-75\%}$ (L/sec)		-0.09	-0.10	0.01	-0.05
(p-value vs. placebo)			(0.898)	(0.188)	(0.544)

[1] For those patients who were able to perform spirometry.
[2] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

8.2.4.4.2.5 Modified Functional Health Status FS-II (R): Health Status FS-II (R) General and FS-II (R) Specific; All Patients Treated, Last Value Carried Forward, Total Population

The patients on budesonide regimens had numerical improvement in both modified FS-II (R) General and Specific scores when compared to patients on placebo. For the mean changes of FS-II (R) General scores from baseline to Week 12, the 0.25 mg QD budesonide group was significantly higher than the placebo group. So was the 0.5 mg QD budesonide group for the mean changes of FS-II (R) Specific scores.

Table 8.2.4.4.2.5. Modified Functional Status-II (R): Child Health Status, FS-II (R) General and FS-II (R) Specific Scores, mean changes from baseline to Week 12; All Patients Treated, Last Value Carried Forward, Total Population. [38:94]

Variable		Placebo	Budesonide Nebulizing Suspension, QD		
			0.25 mg	0.5 mg	1.0 mg
Modified Functional Status-II (R)[1]	n	83	81	73	88
Baseline					
FS-II (R) General		78.1	77.4	75.2	77.4
FS-II (R) Specific		81.9	82.5	80.1	83.2
Mean Change from Baseline[2]					
FS-II (R) General at Week 12		2.5	8.1	6.7	6.8
(p-value vs. placebo)			(0.019)*	(0.085)	(0.064)
FS-II (R) Specific at Week 12		4.6	6.7	9.8	6.7
(p-value vs. Placebo)			(0.392)	(0.039)*	(0.383)

[1] Data sources: [38:186; Section 14.2, Table 17]
[2] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

8.2.4.4.2.6 Child Health Status Questionnaire (RAND-ALL; RAND-1; RAND-2; G-RAND); All Patients Treated, Last Value Carried Forward, Total Population

Patients on budesonide 0.25 mg QD had improved health status scores at Weeks 4 and 12 in comparison to placebo for the RAND-ALL. The differences between this dose group and placebo were statistically significant at both time points.

Table 8.2.4.4.2.6. Child health status: RNAD-ALL Scores, mean changes from baseline to Weeks 4 and 12; All Patients Treated, Last Value Carried Forward, Total Population.

Variable		Placebo	Budesonide Nebulizing Suspension, QD		
			0.25 mg	0.5 mg	1.0 mg
RAND-ALL Scores[1]	n	88	86	75	91
Baseline		56.3	53.9	58.5	57.1
Mean Change from Baseline[2]					
RAND-ALL at Week 4		2.8	7.0	5.0	3.2
(p-value vs. Placebo)			(0.018)*	(0.226)	(0.791)
RAND-ALL at Week 12		4.1	9.7	6.1	7.4
(p-value vs. Placebo)			(0.011)*	(0.370)	(0.123)

[1] Data sources: [38:196; Section 14.2, Table 19]
[2] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

8.2.4.4.2.7 Health Care Utilization; All Patients Treated, Last Value Carried Forward, Total Population

[38:94-5, 200-1]

Compared to the placebo group, children on budesonide did not demonstrate improvement in the health care utilization variables or indirect economic endpoints.

8.2.4.5 Safety Analysis

[38:97-107]

8.2.4.5.1 Extent of Exposure

There were no apparent differences in the exposure to study medication among all treatment groups. [38:98, 241]

8.2.4.5.2 Adverse Events

[38:98-104]

8.2.4.5.2.1 Brief Summary of Adverse Events

There were no deaths reported during the study.

During the baseline phase: There were two SAEs reported in two patients who were not randomized into the double-blind treatment phase (Table 8.2.4.5.2.4). The overall incidence of AEs was 36% for patients in the budesonide groups versus 33% for patients in the placebo group. [38:243-5]

During the treatment phase: A total of 10 SAEs in eight patients were reported (Table 8.2.4.5.2.4). Four patients were discontinued from the treatment phase due to AEs (Table 8.2.4.5.2.5). Each of the SAEs leading to discontinuation from the treatment phase was judged by the investigator to be of unlikely relationship to study treatment.

The number of reported AEs during the treatment phase was similar for the placebo and the three budesonide groups (82% of patients in the budesonide groups, 86% of patients in the placebo group). [38:246] The commonly reported AEs (≥5% of patients in any budesonide group) were similar between the placebo and the budesonide groups (Table 8.2.4.5.2.2).

8.2.4.5.2.2 Display of All Adverse Events

The commonly reported AEs in ≥5% of patients in any budesonide group are summarized in Table 8.2.4.5.2.2.

Reviewer's Comments: 1. The incidence of coughing and pharyngitis was highest in 1.0 mg QD budesonide group suggestive of a dose-response relationship. 2. In AEs with <5% of patients in any budesonide group, there was no apparent difference between the placebo and the budesonide groups.

Table 8.2.4.5.2.2. Summary of most frequently reported AEs (≥5% of patients in any one budesonide treatment group) during the treatment phase. [38:100]

Body System/AE [1]	Placebo	Budesonide Nebulizing Suspension QD			
		0.25 mg	0.5 mg	1.0 mg	Total
n	92	91	83	93	267
Respiratory System Disorders					
Respiratory Infection	41 (45%)	33 (36%)	35 (42%)	32 (34%)	100 (37%)
Sinusitis	13 (14%)	7 (8%)	11 (13%)	14 (15%)	32 (12%)
Rhinitis	9 (10%)	5 (5%)	8 (10%)	13 (14%)	26 (10%)
Coughing	4 (4%)	5 (5%)	7 (8%)	8 (9%)	20 (7%)
Pharyngitis	7 (8%)	4 (4%)	4 (5%)	10 (11%)	18 (7%)
Bronchitis	3 (3%)	3 (3%)	6 (7%)	5 (5%)	14 (5%)
Bronchospasm	4 (4%)	5 (5%)	4 (5%)	4 (4%)	13 (5%)
Body as a Whole					
Fever	26 (28%)	16 (18%)	19 (23%)	21 (23%)	56 (21%)
Accident and/or Injury	10 (11%)	11 (12%)	6 (7%)	8 (9%)	25 (9%)
Resistance Mechanism Disorders					
Otitis Media	11 (12%)	9 (10%)	7 (8%)	7 (8%)	23 (9%)
Infection Viral	3 (3%)	5 (5%)	4 (5%)	2 (2%)	11 (4%)
Gastrointestinal System Disorders					
Gastroenteritis	4 (4%)	4 (4%)	3 (4%)	6 (6%)	13 (5%)
Diarrhea	3 (3%)	4 (4%)	5 (6%)	1 (1%)	10 (4%)
Central & Peripheral Nervous Sys. Disorder					
Headache	9 (10%)	8 (9%)	6 (7%)	10 (11%)	24 (9%)
Hearing & Vestibular Disorders					
Ear Infection NOS	6 (7%)	4 (4%)	6 (7%)	5 (5%)	15 (6%)
Vision Disorders					
Conjunctivitis	5 (5%)	1 (1%)	4 (5%)	3 (3%)	8 (3%)
Platelet, Bleeding & Clotting Disorders					
Epistaxis	-	3 (3%)	4 (5%)	2 (2%)	9 (3%)

[1] Data source: [38:246-51; Section 14.3.1, Table 5]

8.2.4.5.2.3 Analysis of Adverse Events

The frequency of adverse events considered by the investigator to be possibly or probably related to treatment was similar between the placebo and the budesonide groups. [38:252-3]

8.2.4.5.2.4 Serious Adverse Events

There were no deaths reported during this study. A total of 12 SAEs in 10 patients were reported. Two SAEs in two patients were reported during baseline; these patients were not randomized into the study. Ten SAEs in eight patients were reported during the double-blind treatment phase. In all cases the investigator judged the SAE to be unlikely to be related to study treatment, and all events resolved without sequelae.

Table 8.2.4.5.2.4. Summary of serious adverse events.[1] [38:102]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Baseline:		
E-013	Bronchospasm occurring during baseline treatment.	N/A
E-017	Bronchospasm occurring during baseline treatment.	N/A
Placebo:		
18-0331	Bronchospasm/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 0.25 mg, QD:		
09-0160	Bronchospasm/completely recovered.	Unlikely
14-0540	Bronchospasm/completely recovered.	Unlikely
21-0298	Meningitis/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 0.5 mg, QD:		
03-0391	Atelectasis/completely recovered. Hypoxia/completely recovered.	Unlikely Unlikely
10-0434	Bronchospasm/completely recovered. Hypoxia/completely recovered.	Unlikely Unlikely
25-0288	Cellulitis Skin/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 1.0 mg, QD:		
14-0266	Pneumonia/not recovered on day of final visit; completely recovered 13 days later.	Unlikely

[1] Data sources: [38:266-71; Sections 14.3.3.1, 14.3.3.2]
[2] WHO preferred term.

8.2.4.5.2.5 Discontinuations Due to Adverse Events

A total of 4 discontinuations were reported during the treatment phase. All the patients recovered completely with no sequelae.

Table 8.2.4.5.2.5. Summary of discontinuations due to adverse events.[1]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Budesonide Nebulizing Suspension 0.25 mg QD:		
09-0160	Bronchospasm/completely recovered.[3]	Unlikely
21-0298	Meningitis/completely recovered.[3]	Unlikely
Budesonide Nebulizing Suspension 0.5 mg QD:		
10-0434	Bronchospasm/completely recovered.[3]	Unlikely
	Hypoxia/completely recovered.[3]	Unlikely
25-0288	Cellulitis Skin/completely recovered.[3]	Probable

[1] Data sources: [38:265, 270-1]
[2] WHO preferred term.
[3] As confirmed by the investigators following the patient's discontinuation from the study.

8.2.4.5.2.6 Adverse Events of Severe Intensity

[38:257-63]

The incidence of AEs of severe intensity were similar between all four treatment groups. Twenty-one (23%) patients experienced severe AEs in the placebo group and 13 (14%), 17 (20%) and 11 (12%) patients each, in the 0.25, 0.5, and 1.0 mg/day budesonide groups, respectively. Respiratory infection was the most frequently reported severe AE with incidences of 5% in the placebo group compared to 4% in patients on budesonide. Fever occurred in 1% of the budesonide-treated patients compared to 3% of the placebo patients. Severe bronchospasm occurred in 2% of budesonide-treated patients compared to 1% of those receiving placebo. Otitis media occurred in 4% of patients on placebo, with no occurrence in patients treated with budesonide. All other severe AEs were reported with incidences of ≤2%.

8.2.4.5.3 Assessment of HPA-Axis

[38:105-7]

There were no significant differences between the placebo and any budesonide group in test values that would be suggestive of HPA-axis suppression, e.g. the changes in basal or ACTH-stimulated cortisol levels from baseline to Week 12 (Table 8.2.4.5.3A). There were no apparent differences between the placebo and any budesonide group in the numbers of patients showing a shift in responsiveness to ACTH-stimulation from baseline to Week 12 (Table 8.2.4.5.3B).

Table 8.2.4.5.3A . Summary results of ACTH-simulated cortisol tests.[1] [38:106]

Variable			Placebo	Budesonide Nebulizing Suspension, QD		
				0.25 mg	0.5 mg	1.0 mg
ACTH-Stimulated Cortisol Levels (nmol/L)		n				
	Basal		29	26	25	30
	ACTH-Stimulated		26	26	25	30
Basal:	Baseline		289	297	331	351
	Week 12		290	300	285	311
ACTH-Stimulated:	Baseline		656	674	711	703
	Week 12		628	686	714	702
Adjusted Mean Change in ACTH-Stimulated Corticol Levels from Baseline[2]			-32.2	19.8	-11.7	1.6
	(p-value vs. placebo)			(0.275)	(0.667)	(0.460)

[1] Data source: [38:324; Section 14.3.5, Table 4]
[2] Means adjusted for Center Effect.

Table 8.2.4.5.3B. Shifts in ACTH stimulation test from baseline to double-blind treatment phase (Week 12).[1,2] [38:107]

Parameter	Base-line	Placebo n=26		Budesonide Nebulizing Suspension mg/day 0.25 n=25		0.5 n=23		1.0 n=29	
		Abn	Norm	Abn	Norm	Abn	Norm	Abn	Norm
ACTH Stimulation Test[3]	Abn	1	4	1	2	_	2	1	1
	Norm	5	16	2	20	2	19	2	25

[1] Data source: [38:325; 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.

8.2.4.5.4 Evaluation of Clinical Laboratory Tests

[38:104-5]

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. [38:273-309]

8.2.4.5.5 *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. [38:311-23]

8.2.4.5.6 *Assessment Of Oral And Nasal Fungal Cultures*

There were no apparent differences between treatment groups in clinically significant changes in fungal cultures. [38:329-31]

8.2.5 *Conclusions and Comments of Study Results*

This study of budesonide nebulizing suspension once a day was performed in infants and young children aged six months to eight years who had not 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 8.2.5). As with other inhaled steroids, these improvements were not dose-dependent. All three budesonide regimens significantly improved the nighttime and daytime asthma symptom scores and reduced the use of breakthrough medication (short-acting inhaled bronchodilator). However, after adjusting for multiple comparisons using Dunnett's test, only 0.25 mg QD regimen demonstrated significant improvements in primary efficacy variables, i.e., both nighttime and daytime asthma symptom scores; the 0.5 mg QD regimen only significantly improved nighttime symptom score, but not daytime symptom score. For patients who were able to perform PEF and/or spirometry, the 0.5 mg QD regimen significantly improved FEV_1 and FVC. So did the 1 mg QD regimen on FEV_1. All three regimens failed to demonstrate a statistically significant improvement in morning or evening PEF. Only 1.0 mg QD budesonide regimen demonstrated a statistically significant reduction in the proportion of patients who discontinued from the study.

For the health status assessments, significant improvements in the modified Functional Status-II (R) General Score at week 12 and the RAND-ALL Health Index Scores at weeks 4 and 12 were demonstrated in 0.25 mg QD budesonide group. A significant improvement in the modified Functional Status-II (R) Specific Scores at week 12 was demonstrated in 0.5 mg QD budesonide group. For health care utilization variables or indirect economic endpoints, all three budesonide regimens failed to demonstrate a significant improvement. The findings of these variables were not consistent and the clinical relevance of these findings is uncertain.

The safety evaluations did not reveal apparent difference between the treatment groups in reported adverse events, the response to ACTH-stimulation tests, and changes in physical examinations or clinical laboratory tests. In general, the budesonide nebulizing suspension regimens used in this study appeared to be safe.

Of note, only 6 patients in this study were younger than 11 month old and 14 younger than one year old. Same as in Study 04-3100, these were less than the targeted enrollments (n=18 and 21, respectively).

Table 8.2.5. 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, QD		
		0.25 mg	0.5 mg	1.0 mg
Asthma Symptom Score (scale of 0-3):				
Nighttime	-0.16	-0.49	-0.42	-0.42
(p-value vs. placebo)		(0.001)**	(0.010)**	(0.009)*
Daytime	-0.26	-0.57	-0.46	-0.50
(p-value vs. placebo)		(0.002)**	(0.049)*	(0.016)*
Use of Breakthrough Medicine (days)	-4.19	-6.26	-6.31	-5.98
(p-value vs. Placebo)		(0.017)*	(0.018)*	(0.038)*
PEF (L/min)[3]:				
Morning	7.1	14.4	6.5	10.9
(p-value vs. placebo)		(0.135)	(0.901)	(0.417)
Evening	3.6	11.2	3.8	9.9
(p-value vs. placebo)		(0.114)	(0.977)	(0.169)
Spirometry[3]:				
FEV_1 (L)	-0.07	-0.01	0.03	0.03
(p-value vs. placebo)		(0.216)	(0.044)*	(0.033)*
FVC (L)	-0.04	0.05	0.06	0.04
(p-value vs. placebo)		(0.060)	(0.038)*	(0.094)
$FEF_{25-75\%}$ (L/sec)	-0.09	-0.10	0.01	-0.05
(p-value vs. placebo)		(0.898)	(0.188)	(0.544)
Proportion of Patients Discontinued (%)	28	19	24	14
(p-value vs. placebo)[4]		(0.163)	(0.607)	(0.020)*

[1] Data sources: Tables 8.2.4.1, 8.2.4.4.1.1, 8.2.4.4.2.1A, 8.2.4.4.2.3-4, 8.2.4.4.2.6-7.

[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] For those patients who were able to perform the test.

[4] 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).

8.3 Study 04-3072: A Study of Three Dose Levels of Budesonide (Pulmicort) Nebulizing Suspension and Placebo in Asthmatic Children Aged Between Four and Eight Years.

8.3.1 Objectives

[52:13]
The objectives of this study were to compare the relative efficacy and safety of budesonide nebulizing suspension, 0.25 mg, 0.5 mg, and 1.0 mg administered twice a day, versus placebo, in inhaled corticosteroid-dependent asthmatic patients aged four to eight years.

8.3.1.1 Primary Efficacy Variables

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

- The primary efficacy variables were the mean change from baseline in nighttime and daytime asthma symptom scores over the 12-week treatment phase.

8.3.1.2 Secondary Efficacy Variables

- 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 number of days breakthrough medication (short-acting inhaled bronchodilator) and the amount that was used.
- Spirometry test variables (FEV_1, $FEF_{25-75\%}$ and FVC) performed at clinic visits.
- PEF measured daily in the morning and evening.

8.3.1.3 Safety Variables

- Reported adverse events (AEs).
- Pre- and post-ACTH-stimulation effects on HPA-axis function.
- Changes in physical examinations, vital signs, and clinical laboratory tests (including oropharyngeal and nasal fungal cultures).

8.3.2 Design

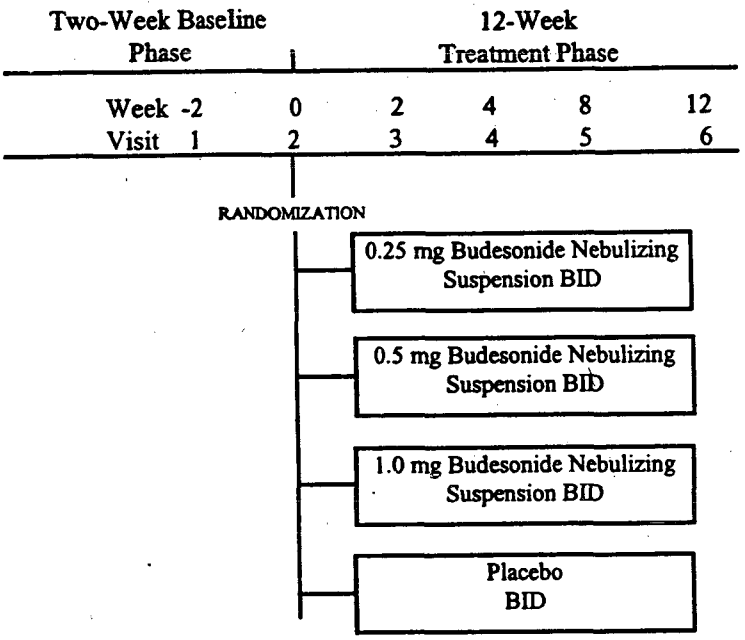
[52:14-7]
This was a multicenter randomized, double-blind, placebo-controlled, parallel-group study. A total of 178 patients were randomized at 17 centers located throughout the USA.

Eligible patients initially entered a two-week baseline phase, which was followed by a 12-week treatment phase. On entry into the study (Visit 1) patients underwent several screening evaluations and were provided with a diary card to record on a daily basis nighttime and daytime asthma symptom scores, and daily use of bronchodilator therapy and morning and evening PEFs. At the end of the baseline phase (Visit 2) eligible patients discontinued taking their inhaled corticosteroids and were randomized to receive one of the following treatments:

- budesonide nebulizing suspension, 0.25 mg BID in the morning and evening
- budesonide nebulizing suspension, 0.50 mg BID in the morning and evening
- budesonide nebulizing suspension, 1.0 mg BID in the morning and evening
- placebo in the morning and evening

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

Figure 8.3.2. Study Design. [52:15]



8.3.3 Protocol

The protocol of this study was similar to that of Study 04-3100. In this study, only budesonide BID regimens were studied and only inhaled corticosteroid-dependent asthmatic patients aged four to eight were recruited.

8.3.3.1 Selection of Study Population

[52:17-9]

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

8.3.3.1.1 Inclusion Criteria

Same as those in Study 04-3100 (Section 8.1.3.1.1) except the following modifications and/or addition:

- Male or female outpatients between 4 and 8 years (instead of 6 months and 8 years) of

age at screening.

- Daily use of an inhaled steroid for at least 3 months prior to Visit 1.
- No long-acting inhaled β_2-agonists within 14 days (instead of 7 days) prior to Visit 1.
- Patients must have had a basal $FEV_1 \geq 50\%$ of predicted, and reversibility of $\geq 15\%$ at 15 ± 5 minutes after a standard dose of inhaled bronchodilator (albuterol).

8.3.3.1.2 Exclusion Criteria

Same as those in Study 04-3100 (Section 8.1.3.1.2).

8.3.3.2 Study Drugs

[52:20]
Same as those in Study 04-3100 (Section 8.1.3.2).

8.3.3.3 Prior and Concomitant Treatments

[52:23]
Same as those in Study 04-3100 (Section 8.1.3.3) except the following modifications and/or addition:

- No long-acting inhaled β_2-agonists within 14 days (instead of 7 days) prior to Visit 1.
- During the baseline phase, the patient must be on a stable dose of the same inhaled steroid.

8.3.3.4 Efficacy Measurements and Variables

[52:24-9]
Same as those in Study 04-3100 (Table 8.1.2, Sections 8.1.3.4 - 8.1.3.4.2) except the modifications and/or addition described in Section 8.3.3.4.1-2.

8.3.3.4.1 Procedures at the Clinic

Same as those in Study 04-3100 (Section 8.1.3.4.1) except the following modifications and/or addition:

- Spirometry testing was performed at all visits in all patients (instead of only patients capable of performing this procedure).
- Each patient (instead of only patients capable of using a PEF meter) was issued a [redacted] peak flow meter, and instructed on its proper use and care (Visit 1).

8.3.3.4.2 Assessments at Home

Same as those in Study 04-3100 (Section 8.1.3.4.2) except the following modifications and/or addition:

- Each patient (instead of only patients capable of using a PEF meter) performed morning and evening PEF measurements every day.

8.3.3.5 Safety Measurements and Variables

[52:24-9]

8.3.3.5.1 Procedures at the Clinic

Same as those in Study 04-3100 (Section 8.1.3.5.1).

8.3.3.6 Adverse Events (AEs)

[52:29-31]

Same as those in Study 04-3100 (Sections 8.1.3.6 - 8.1.3.6.3).

8.3.3.7 Treatment and Measurement Discontinuation

[52:19-20]

Same as those in Study 04-3100 (Section 8.1.3.7).

8.3.3.8 Statistical Analysis

[52:33-8]

8.3.3.8.1 Analytical Plan

Same as those in Study 04-3100 (Section 8.1.3.8.1).

8.3.3.8.2 Handling of Dropouts

Same as those in Study 04-3100 (Section 8.1.3.8.2).

8.3.3.8.3 Statistical Methods

8.3.3.8.3.1 Statistical Methods: Efficacy Variables

8.3.3.8.3.1.1 Primary Efficacy Variables - Nighttime And Daytime Asthma Symptom Scores

[52:35-7]

Same as those in Study 04-3100 (Section 8.1.3.8.3.1.1) except the following modifications and/or addition:

- Step-down contrasts as proposed by Dunnett and Tamhane were used to determine the minimal effective dose (MED).
- A comparison between the highest and the lowest dose budesonide groups was performed to assess if an overall dose response relationship existed. If a dose-response relationship existed, the dose-response curve would be characterized using a parametric regression model including both linear and quadratic terms for dose level

8.3.3.8.3.1.2 Secondary Efficacy Variables - Treatment Failures and Use of Breakthrough Medication

Same as those in Study 04-3100 (Section 8.1.3.8.3.1.2).

8.3.3.8.3.1.3 Secondary Efficacy Variables - FEV_1, FVC, $FEF_{25-75\%}$, Evening and Morning PEFs

Same as those in Study 04-3100 (Section 8.1.3.8.3.1.3).

8.3.3.8.3.2 Statistical Methods: Safety Variables

Same as those in Study 04-3100 (Section 8.1.3.8.3.2).

8.3.4 Results

8.3.4.1 Patient Disposition

[52:39-41]

The first patient was enrolled into the study in May, 1994. The last patient completed the study in November, 1996. A total of 220 patients were screened. Of these, 42 patients were not randomized. The most frequent reason for patients discontinuing from the baseline phase was failure to fulfill the randomization criteria for asthma symptoms and use of bronchodilator for at least 5 of the 7 days prior to randomization (40 % of patients). [52:67-9]

A summary of patient disposition for 178 randomized patients is presented in Table 8.3.4.1. A total of 39 patients were discontinued from the treatment phase of the study. The proportion of patients who were discontinued from the placebo group (43%) was greater than that for the budesonide groups (13-20%). The proportion of patients in the placebo group discontinuing due to worsening asthma (36%) was also greater than that for the budesonide groups (2-13%).

All 178 randomized patients were included in APT analyses. One patient, who took long term steroid, was judged to be completely non-evaluable for the Per Protocol analysis and 35 were partially evaluable. The most frequent reason for partial non-evaluability was "patient took short-term steroid." [52:75-7]

Table 8.3.4.1. Summary of patient disposition. [52:0.4]

Number of Patients	Placebo	Budesonide Nebulizing Suspension BID		
		0.25 mg	0.5 mg	1.0 mg
Randomized	44	47	42	45
Completed Double-Blind Treatment	25 (57%)	41 (87%)	37 (88%)	36 (80%)
Total No. Patients Discontinued:	19 (43%)	6 (13%)**	5 (12%)**	9 (20%)*
Worsening Asthma[1]	16 (36%)	5 (11%)**	1 (2%)***	6 (13%)*
Adverse Event	2 (5%)	0 (0%)	1 (2%)	2 (4%)
Use of Medication Excluded by Protocol[2]	1 (2%)	1 (2%)	1 (2%)	0 (0%)
Non-Compliance w/Study Procedures	0 (0%)	(0%)	2 (5%)	1 (2%)
Evaluated for Efficacy Analyses APT/PP[3]	44/43	47/47	42/42	45/45
Evaluated for Safety	44	47	42	45

[1] Includes patients who were discontinued due to lack of therapeutic effect or disease deterioration and patients who received steroid medication(s) for worsening asthma not permitted by the protocol.

[2] Steroid medications for reasons other than worsening of asthma, i.e., hives and croup.

[3] Individual patient data were partially excluded from per protocol efficacy calculations for 18, 5, 4 and 8 patients in the placebo, 0.25 mg BID, 0.5 mg BID and 1.0 mg BID groups, respectively.

Data Source: [52:71-3; Section 14.1.1, Tables 4-5]

*p ≤ 0.050, **p ≤0.010, *** p ≤0.001 versus placebo.

8.3.4.2 Demographic and Other Baseline Characteristics

[38:82-3]

The basic demographic characteristics of the study population are summarized in Table 8.3.4.2. Except the gender, the basic demographic characteristics were similar for the four treatment groups.

Table 8.3.4.2. Demographic characteristics. [52:43]

Variable	Placebo	Budesonide Nebulizing Suspension BID			
		mg BID	0.5 mg BID	1.0 mg BID	Total
n	44	47	42	45	178
Gender:					
Male	20 (45.5%)	31 (66.0%)	30 (71.4%)	29 (64.4%)	110 (61.8%)
Female	24 (54.5%)	16 (34.0%)	12 (28.6%)	16 (35.6%)	68 (38.2%)
Age (months):					
Mean ± SD	80.7 ± 18.1	78.3 ± 15.0	82.2 ± 16.5	81.4 ± 15.1	80.6 ± 16.1
Range	48-108	48-107	48-106	49-107	48-108
Race:					
Caucasian	37 (84.1%)	38 (80.9%)	35 (83.3%)	40 (88.9%)	150 (84.3%)
Black	6 (13.6%)	7 (14.9%)	3 (7.1%)	2 (4.4%)	18 (10.1%)
Hispanic	1 (2.3%)	2 (4.3%)	2 (4.8%)	3 (6.7%)	8 (4.5%)
Other	0 (0.0%)	0 (0.0%)	2 (4.8%)	0 (0.0%)	2 (1.1%)
Weight : Mean ± SD					
Kilograms	24.7 ± 6.7	24.1 ± 6.4	26.5 ± 7.6	25.2 ± 6.4	25.1 ± 6.8
Pounds	54.5 ± 14.7	53.2 ± 14.1	58.5 ± 16.9	55.6 ± 14.2	55.4 ± 15.0
Height (cm):					
Mean ± SD	120.8 ±10.2	119.8 ±7.9	124.0 ±11.1	121.7 ±10.4	121.5 ±10.0

Data Source: [52:79-82; Section 14.1.2, Table 1]

Reviewer's Comments: The male to female ratio of each group is typical of asthma patients in this age range except the placebo group, which had more females (54.5%) than males (45.5%). The effect of this on efficacy variables is uncertain.

8.3.4.2.1 Baseline Asthma Symptom Scores and Pulmonary Function Test Data

[52:43-4, 79-82]

The mean duration of asthma at entry into the study, baseline asthma symptom scores, FEV_1 and PEF data are summarized in Table 8.3.4.2.1.

Table 8.3.4.2.1. Baseline lung function and asthma symptom scores. [52:44]

Variable	Placebo	Budesonide Nebulizing Suspension BID			
		0.25 mg BID	0.5 mg BID	1.0 mg BID	Total
n	44	47	42	45	178
Duration of Asthma (months)					
Mean±SD	49.8±26.6	51.8± 21.0	48.1±23.4	53.1±19.2	50.8 ± 22.5
Range	6-102	13-92	6-94	11-100	6-102
Nighttime Asthma Symptom Scores: Mean±SD	1.18±0.55 n=44	1.10±0.60 n=47	1.04±0.66 n=42	1.08±0.58 n=44	1.10±0.59 n=177
Daytime Asthma Symptom Scores: Mean±SD	1.33±0.50 n=44	1.35±0.46 n=47	1.33±0.50 n=42	1.35±0.54 n=45	1.34±0.50 n=178
FEV_1: Mean± SD	1.14±0.29	1.13±0.33	1.20±0.33	1.18 ±0.34	1.16±0.32
% Predicted	79.2±10.9	80.5±15.8	78.8±16.0	80.2±15.0	79.7±14.5
% Reversibility	30.3±16.9 n=44	35.9±17.4 n=47	36.2±17.7 n=42	32.3±18.8 n=45	33.7±17.7
Morning PEF (L/min):					
Mean±SD	158.3±44.6	155.6±44.9	162.1±53.4	167.6±67.6	160.8±53.1
Evening PEF (L/min):					
Mean±SD	164.7±44.5	160.9±46.6	171.6±55.6	169.9±67.2	166.7±53.9

Data Source: [52:79-82; Section 14.1.2, Table 1]

Reviewer's Comments: There were no significant differences between the treatment groups for any of these variables.

8.3.4.2.2 *Baseline Physical Examination, Previous and Concomitant Diseases*

[52:44, 83-7]

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

The treatment groups were similar with respect to concomitant diagnoses present at baseline. Sixty-seven percent of the patients had allergic rhinitis. Chronic rhinitis, chronic sinusitis, dermatitis, headache, and otitis media were reported in 8-13% of the study population. Other concomitant diseases were present in 7% or fewer of the patients. The most frequently reported past diagnosis was otitis media (31%).

8.3.4.2.3 *Prior and Concomitant Medications*

[52:45-6; Amendment 2/5/98]

8.3.4.2.3.1 Asthma Medications

Prior asthma medications: The treatment groups were similar with respect to the prior use of asthma drugs. All of the patients randomized had used asthma medications before enrollment in the study. The asthma medications most frequently used prior to the study were albuterol (oral/inhaled salbutamol; 97%), beclomethasone (59%), cromolyn sodium (41%), triamcinolone (29%), prednisolone (20%), flunisolide (14%) and theophylline (10%). [52:88-9]

Concomitant asthma medications: The β_2-agonists was the most common concomitant asthma medication, with 96% of patients receiving oral/inhaled albuterol at some time during the treatment phase. Thirty-nine percent of the patients received parenteral/oral steroids, and 45% received other anti-inflammatory agents. [Amendment 2/5/98: Section 14.1.2, Tables 7-8]

8.3.4.2.3.2 Non-Asthma Medications

Prior non-asthma medications: The prior use of non-asthma medications was similar among treatment groups. Drug classes mentioned most frequently were antipruritics (67%), nasal preparations (54%), systemic antihistamines (29%), systemic antibacterials (24%), analgesics (16%), cough and cold preparations (11%), and allergens (8%). [52:92-7]

Concomitant non-asthma medications: The use of concomitant non-asthma medications was similar among treatment groups. Drug classes mentioned most frequently were antipruritics (69%), nasal preparations (63%), systemic antibacterials (52%), analgesics (39%), systemic antihistamines (38%), cough and cold preparations (22%), allergens (8%), and dermatological corticosteroids (7%). [Amendment 2/5/98: Protocol 04-3072, Section 14.1.2, Tables 11-2]

Reviewer's Comments: The data of concomitant asthma and non-asthma medications on the original submission were incorrect. The sponsor provided the correct data in the amendment dated 2/5/98.

8.3.4.3 Efficacy Analysis

8.3.4.3.1 Primary Efficacy Variables

[52:46-51]

8.3.4.3.1.1 Asthma Symptom Scores; All Patients Treated, Last Value Carried Forward, Total Population

Table 8.3.4.3.1.1. Asthma symptom scores; All Patients Treated, Last Value Carried Forward, Total Population. [52:46]

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension, BID		
		0.25 mg	0.5 mg	1.0 mg
Asthma Symptom Score (scale of 0-3):[1]				
Mean Change from Baseline[2]				
n	44	47	42	44
Nighttime	-0.08	-0.36	-0.37	-0.36
(p-value vs. placebo)		(0.022)**	(0.021)*	(0.026)**
n	44	47	42	45
Daytime	-0.11	-0.45	-0.53	-0.55
(p-value vs. placebo)		(0.012)**	(0.003)**	(0.002)**

[1] Data sources: [52:105-8; Section 14.2, Table 1]

[2] Mean change adjusted for center effect.

* 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.

For nighttime asthma symptom scores, the adjusted mean changes from baseline to Weeks 0-12 in patients of the three budesonide groups were statistically significantly greater compared to placebo ($p \leq 0.026$). When the Dunnett's adjustment was applied, the 0.25 mg and 1.0 mg BID budesonide groups maintained their superiority over the placebo group. This is shown graphically in Figure 8.3.4.3.1.1A.

For daytime asthma symptom scores, the adjusted mean changes from baseline to Weeks 0-12 in patients of the three budesonide groups were statistically significantly greater compared to placebo ($p \leq 0.012$). When the Dunnett's adjustment was applied, all three budesonide groups maintained superiority over the placebo group. This is shown graphically in Figure 8.3.4.3.1.1B.

Reviewer's Comments: The improvements in asthma symptom scores were not dose-dependent.

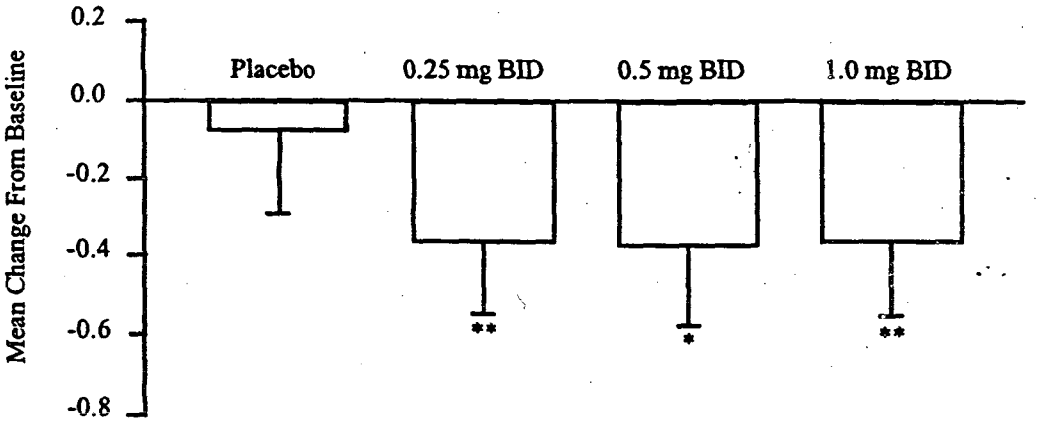
Compared to the placebo group, the improvement in nighttime and daytime asthma symptom scores of each budesonide group was observed by Week 2 (with the exception of nighttime symptom score of 0.50 mg budesonide BID group; by Week 4) and was sustained throughout the 12-week treatment phase. This is shown graphically in Figure 8.3.4.3.1.1C and D. [52:105, 107]

Reviewer's Comments: However, when comparing each individual budesonide group to placebo, the differences in the adjusted mean changes of either nighttime or daytime symptom scores were not statistically significant in all three budesonide groups until Weeks 4-6.

If the time to onset responses is defined as the first day associated with a statistically significant difference in changes from the baseline of asthma symptom scores between the budesonide and placebo treatment groups, statistically significant differences for nighttime asthma symptom scores between all budesonide groups combined compared to placebo were observed on Day 8 ($p<0.050$) and that for daytime asthma symptom scores on Day 3 ($p<0.050$). [Amendment 1/7/98]

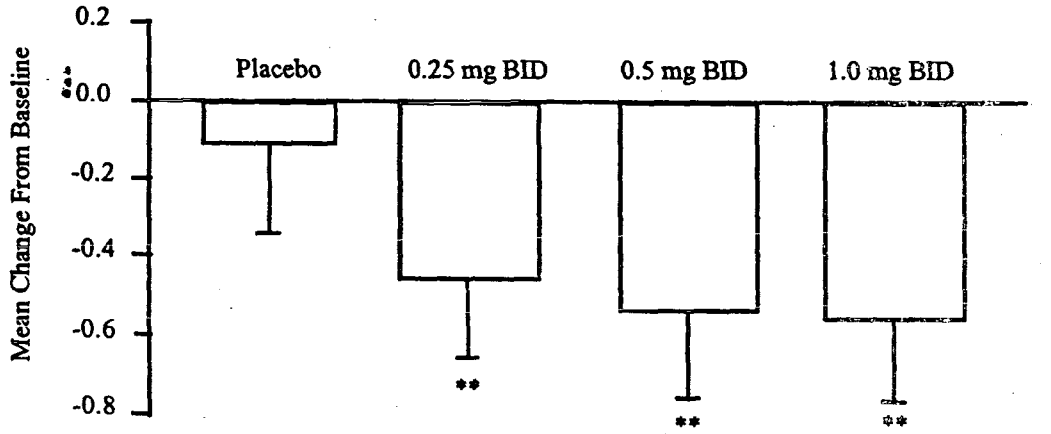
Reviewer's Comments: While the above separations from placebo were observed, the differences in changes of nighttime asthma symptom scores between the budesonide and placebo groups were not statistically significant in any of the first 14 days of treatment phase (except Day 8). In contrast, the significant differences in changes of daytime asthma symptom scores were maintained in most of the first 14 days (except Days 12 and 14).

Figure 8.3.4.3.1.1A. Mean change[1] from baseline to double-blind treatment (Weeks 0-12) in nighttime asthma symptom scores ±95% C.I.; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [52:48]



[1] Means adjusted for center effect.
* p≤0.05 versus placebo level before Dunnett's adjustment.
** p≤0.05 versus placebo level before and after Dunnett's adjustment.

Figure 8.3.4.3.1.1B. Mean change[1] from baseline to double-blind treatment (Weeks 0-12) in daytime asthma symptom scores ±95% C.I.; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [52:48]



[1] Means adjusted for center effect.
* p≤0.05 versus placebo level before Dunnett's adjustment.
** p≤0.05 versus placebo level before and after Dunnett's adjustment.

Figure 8.3.4.3.1.1C. Summary of mean nighttime asthma symptom scores; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [52:49]

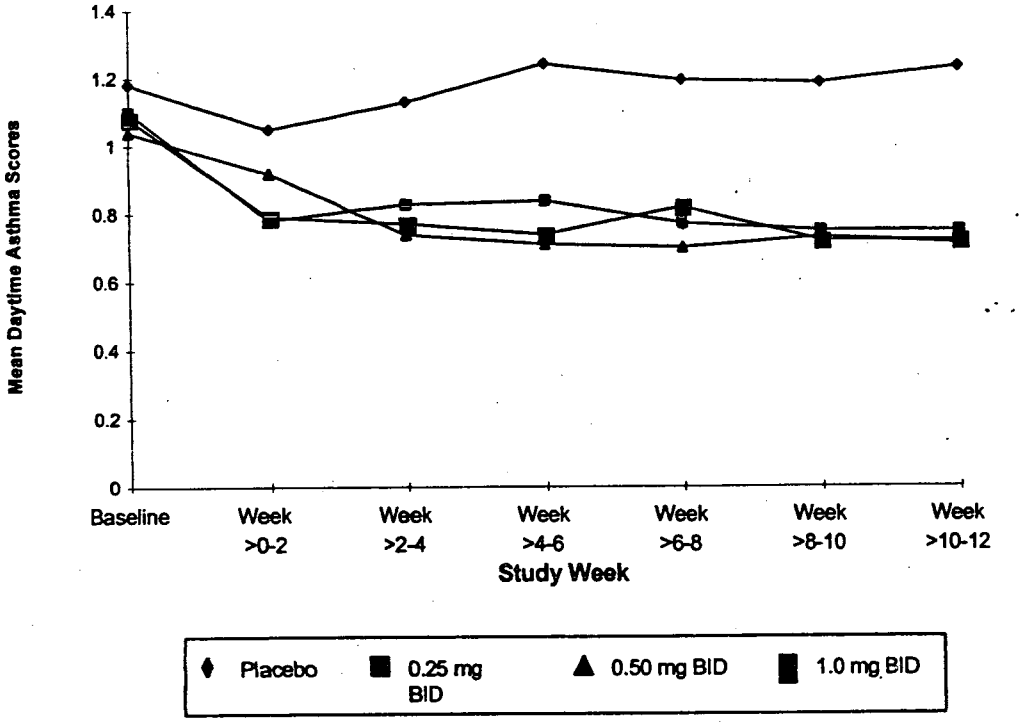
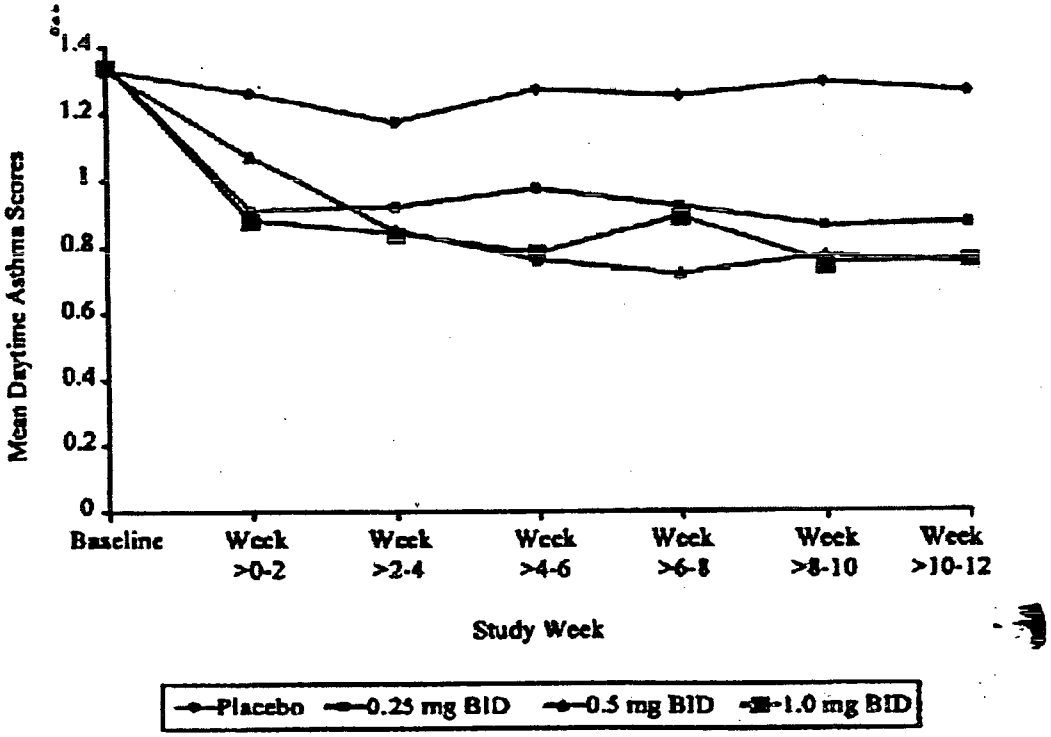


Figure 8.3.4.3.1.1D. Summary of mean daytime asthma symptom scores; All Patients Treated Analysis, Last Value Carried Forward, Total Population. [52:0.6]



8.3.4.3.1.2 Nighttime and Daytime Asthma Symptom Scores, by Baseline Symptom Severity Score; All Patients Treated, Last Value Carried Forward

In each budesonide group, the patients whose symptoms were most severe at baseline showed a higher degree of improvement than those who were judged mild or moderate at baseline. However, the number of patients classified in the severe category was very small (n=10). [52:123-4]

8.3.4.3.1.3 Nighttime and Daytime Asthma Symptom Scores, Summary of Changes (Improved; No Change; Worse), Baseline to Double-Blind Treatment Phase; All patients Treated, Last Value Carried Forward

For both nighttime and daytime asthma symptom scores, the proportion of patients classified as having improved by at least 0.5 points in the budesonide groups was higher compared to the placebo group. [52:126-7]

For nighttime symptom scores, 31-34% of the patients treated with budesonide were classified as having improved by at least 0.5 points compared to 14% for placebo. Four to 9% of the patients on budesonide were classified as having worsened by at least 0.5 points compared to 11% for placebo. Fifty-seven to 62% of the patients on budesonide were classified as having no change (-0.5 points < change < 0.5 points) compared to 75% for placebo.

For daytime asthma symptom scores, 47-57% of the patients treated with budesonide showed improvement compared to 23% for placebo. Four to 7% of the patients on budesonide were classified as having worsened compared to 9% for placebo. Thirty-six to 47% of the patients on budesonide were classified as having no change (-0.5 points < change < 0.5 points) compared to 68% for placebo.

Reviewer's Comments: Altogether, more than half of patients on budesonide were classified as having no change or having worsened in asthma symptom scores (67% for nighttime scores and 49% for daytime scores).

8.3.4.3.1.4 Nighttime and Daytime Asthma Symptom Scores; All Patients Treated, Observed Cases, or Per Protocol (Excluding All Patients with Major Violations of the Protocol)

The results of these analyses showed a similar trend of improvement in asthma symptom scores in budesonide groups as that of the APT, LVCF analysis. [52:121-2]

Reviewer's Comments: However, by per protocol analysis, statistically significant improvements were observed only in 0.5 mg and 1.0 mg BID budesonide groups for daytime symptom scores. No budesonide group demonstrated a statistically significant improvement in nighttime scores compared to placebo.

8.3.4.3.2 Secondary Efficacy Variables

[52:51-3]

8.3.4.3.2.1 Use of Breakthrough Medication; All Patients Treated, Last Value Carried Forward, Total Population

Patients on budesonide showed reduced use of breakthrough medication from baseline to the treatment phase compared to placebo. The differences between each budesonide regimen and placebo were statistically significant ($p \leq 0.032$).

Table 8.3.4.3.2.1A. Use of breakthrough medication, mean changes from baseline in the number of days patients took breakthrough medication; All Patients Treated, Last Value Carried Forward, Total Population. [52:52]

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension, BID		
		0.25 mg	0.5 mg	1.0 mg
Use of Breakthrough Medicine[1]				
n	44	47	42	45
Baseline	11.8	11.6	12.0	10.8
Mean Change from Baseline[2]	-3.14	-5.56	-6.66	-6.00
(p-value vs. Placebo)		(0.032)*	(0.002)*	(0.012)*

[1] Data source: [52:129; Section 14.2, Table 14]
[2] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

Patients on budesonide showed reduced use of breakthrough medication (as the number of puffs or nebulizations used per day) from baseline to the treatment phase compared to placebo.

Table 8.3.4.3.2.1B. Amount of breakthrough medication used; All Patients Treated, Last Value Carried Forward, Total Population. [52:130]

Variable (Weeks 1-12)	Placebo	Budesonide Nebulizing Suspension, BID		
		0.25 mg	0.5 mg	1.0 mg
Use of nebulizer				
n	14	21	15	13
Baseline[1]	1.91	1.79	2.00	1.18
Mean Change from Baseline[1]	-0.04	-0.96	-1.33	-0.72
Use of pMDI				
n	29	26	26	32
Baseline[1]	3.10	2.93	3.30	2.85
Mean Change from Baseline[1]	-0.15	-1.10	-1.72	-1.51

[1] The number of puffs (≠ doses) or nebulizations of breakthrough medication used per day; not adjusted for center effect.

Reviewer's Comments: The reduction in use of breakthrough medication (days, puffs of pMDI/day, or nebulizations/day) was not dose dependent.

8.3.4.3.2.2 Proportion of Patient Discontinuations from the Study

See Section 8.3.4.1.

8.3.4.3.2.3 Morning and Evening PEFs; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that Could Perform The Maneuver

For morning PEF, the differences between each budesonide group and placebo were statistically significant ($p \leq 0.030$). For evening PEF, the numerical improvement was observed in all budesonide groups compared to placebo, but statistical significance was reached only in the 0.25 mg BID treatment group ($p = 0.042$).

Table 8.3.4.3.2.3. Mean changes from baseline in morning PEF; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that could perform the maneuvers. [52:132, 137]

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension, BID		
		0.25 mg	0.5 mg	1.0 mg
PEF[1]: n	44	47	42	45
Mean Change from Baseline (L/min)[1]				
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)

[1] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

Reviewer's Comments: The improvement in morning or evening PEF was not dose dependent.

8.3.4.3.2.4 FEV_1, FVC and Corresponding $FEF_{25-75\%}$; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that Could Perform The Maneuvers

Except FEV_1 and $FEF_{25-75\%}$ for the 0.5 mg BID budesonide group and $FEF_{25-75\%}$ for the 1.0 mg BID group, there were no significant differences in the mean changes from baseline in FEV_1, FVC or $FEF_{25-75\%}$ between each budesonide group and placebo.

Table 8.3.4.3.2.4. Mean changes from baseline in FEV_1, FVC and Corresponding $FEF_{25-75\%}$; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that could perform the maneuvers. [52:137]

Variable (Weeks 0-12)		Placebo	Budesonide Nebulizing Suspension, BID		
			0.25 mg	0.5 mg	1.0 mg
Spirometry:	n	41	46	42	45
Mean Change from Baseline[1]					
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)*

[1] For those patients who were able to perform spirometry.
[2] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

8.3.4.4 Safety Analysis

[52:55-64]

8.3.4.4.1 Extent of Exposure

The mean number of days exposure to study drug for the patients in each budesonide group (77-81 days) was higher compared to placebo (64 days).

Reviewer's Comments: This was likely due to that the proportion of patients who were discontinued from the placebo group (43%) was greater than that for the budesonide groups (13-20%). Most of these patients were discontinued from the study due to worsening asthma. (Section 8.3.4.1) This may not have significant effect on the analysis of efficacy variables.

8.3.4.4.2 Adverse Events

[52:55-64]

8.3.4.4.2.1 Brief Summary of Adverse Events

There were no deaths reported during the study.

During the baseline phase: There were two SAEs reported in two patients (Table 8.3.4.4.2.4). The overall incidence of AEs was 23% for patients in the budesonide groups versus 30% for patients in the placebo group. [52:166]

During the treatment phase: A total of two SAEs in two patients were reported (Table 8.3.4.4.2.4). Five patients were discontinued from the treatment phase due to AEs (Table 8.3.4.4.2.5). Of all of the SAEs and adverse events leading to discontinuation

from the treatment phase, only one was judged to be possibly related to study treatment.

The number of reported AEs during the treatment phase was similar for the placebo and the three budesonide groups (80% of patients in the budesonide groups, 86% of patients in the placebo group). The most commonly reported AEs in both placebo and budesonide groups were respiratory infection, sinusitis, rhinitis, and fever (Table 8.3.4.4.2.2).

8.3.4.4.2.2 Display of All Adverse Events

The commonly reported AEs in ≥5% of patients in any budesonide group are summarized in Table 8.3.4.4.2.2.

Table 8.3.4.4.2.2. Summary of most frequently reported AEs (≥5% of patients in any one budesonide treatment group) during the treatment phase. [52:57]

	Placebo	Budesonide Nebulizing Suspension BID			
		0.25 mg	0.5 mg	1.0 mg	Total
n	44	47	42	45	134
Body System/AE [1]					
Respiratory System Disorders					
Respiratory Infection	15 (34%)	17 (36%)	16(38%)	17 (38%)	50 (37%)
Sinusitis	8 (18%)	6 (13%)	4 (10%)	7 (16%)	17 (13%)
Rhinitis	4 (9%)	7 (15%)	5 (12%)	5 (11%)	17 (13%)
Coughing	1 (2%)	6 (13%)	4 (10%)	3 (7%)	13 (10%)
Pharyngitis	4 (9%)	3 (6%)	5 (12%)	3 (7%)	11 (8%)
Body as a Whole					
Fever	8 (18%)	7 (15%)	5 (12%)	4 (9%)	16 (12%)
Flu-Like disorder	0 (0%)	0 (0%)	2 (5%)	2 (4%)	4 (3%)
Accident and/or Injury	2 (5%)	2 (4%)	0 (0%)	4 (9%)	6 (4%)
Resistance Mechanism Disorders					
Otitis Media	2 (5%)	5 (11%)	1 (2%)	3 (7%)	9 (7%)
Moniliasis	0 (0%)	0 (0%)	4 (10%)	1 (2%)	5 (4%)
Gastrointestinal System Disorders					
Gastroenteritis	1 (2%)	3 (6%)	1 (2%)	3 (7%)	7 (5%)
Vomiting	3 (7%)	1 (2%)	3 (7%)	0 (0%)	4 (3%)
Central & Peripheral Nervous Sys. Disorder					
Headache	2 (5%)	7 (15%)	2 (5%)	4(9%)	13 (10%)
Hearing & Vestibular Disorders					
Earache	1 (2%)	0 (0%)	2 (5%)	0 (0%)	2 (1%)
Ear Infection NOS	1 (2%)	1 (2%)	2 (5%)	1 (2%)	4 (3%)
Vision Disorders					
Conjunctivitis	0 (0%)	3 (6%)	0 (0%)	0 (0%)	3 (2%)
Skin & Appendages Disorders					
Rash	1 (2%)	3 (6%)	0 (0%)	0 (0%)	3 (2%)

[1] Data source: [52:170-2; Section 14.3.1, Table 6]

Reviewer's Comments: In general, the commonly reported AEs were similar between placebo and the budesonide groups. Of note, coughing, moniliasis, and headache were observed more frequently in the budesonide groups than the placebo, which could be related to budesonide treatment. 2. In AEs with <5% of patients in any budesonide group, there was no apparent difference between the placebo and the budesonide groups.

8.3.4.4.2.3 Analysis of Adverse Events

There was no apparent difference between the placebo and the budesonide groups in the frequency of adverse events considered by the investigator to be possibly or probably related to treatment. The incidence of coughing or moniliasis was higher in the budesonide groups compared to placebo (3 and 0%, respectively, for either AE). [52:173]

8.3.4.4.2.4 Serious Adverse Events

There were no deaths reported during this study. A total of 4 SAEs in 4 patients were reported. Two SAEs in two patients were reported during baseline. One patient was later re-screened and successfully randomized. The other patient was discontinued from the study. Two SAEs in 2 patients were reported during the double-blind treatment phase. In both cases the investigator judged the SAE to be unlikely to be related to study treatment.

Table 8.3.4.4.2.4. Summary of serious adverse events.[1]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Baseline:		
02-E013	Bronchospasm/completely recovered.	N/A
02-E005	Bronchospasm/completely recovered.	N/A
Placebo:		
05-2103	Lymphadenopathy/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 0.5 mg, BID:		
18-0414	Fracture/completely recovered.	Unlikely

[1] Data sources: [52:176, 181-2]
[2] WHO preferred term.

8.3.4.4.2.5 Discontinuations Due to Adverse Events

A total of 5 discontinuations were reported during the treatment phase. All the patients recovered completely with no sequelae.

Table 8.3.4.4.2.5. Summary of discontinuations due to adverse events.[1]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Placebo:		
05-0213	Lymphadenopathy/completely recovered.	Unlikely
14-0102	Otitis media/completely recovered.	Unlikely
	Sinusitis/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 0.5 mg BID:		
04-0117	Chest pain/completely recovered.	Possible
Budesonide Nebulizing Suspension 1.0 mg BID:		
06-0165	Rhinitis/completely recovered.	Unlikely
	Sinusitis/completely recovered.	Unlikely
09-0142	Respiratory infection/completely recovered.	Unlikely

[1] Data sources: [52:180, 182-4]
[2] WHO preferred term.

8.3.4.4.2.6 Adverse Events of Severe Intensity

[52:177-8]

Six patients experienced AEs of severe intensity in the placebo group and 2, 5 and 3 patients each, in the 0.25, 0.5, and 1.0 mg BID budesonide groups, respectively. Respiratory infection was the most frequently reported severe AE with incidences of 2% in the placebo group compared to 4% in total patients on budesonide. Bronchitis and sinusitis occurred in 5% of patients on placebo with no occurrence in patients treated with budesonide. Stridor occurred in <1% of budesonide-treated patients compared to 2% of those receiving placebo. All other severe AEs were reported with incidences of ≤2%.

8.3.4.4.3 Assessment of HPA-Axis

[52:62-3]

There were no consistent differences between the placebo and any budesonide group in test values that clearly indicated a HPA-axis suppression (Table 8.3.4.4.3A). There were no apparent differences between the placebo and any budesonide group in the numbers of patients showing a shift in responsiveness to ACTH stimulation from baseline to Week 12 (Table 3.3.4.4.3B).

Reviewer's Comments: Of note, 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). The significance of this finding is uncertain but does suggest a measurable systemic effect of nebulized budesonide.