All changes in the subject's ordinary medication, e.g., dose change or new added medication, were recorded in the CRF. Reasons for changes in medication which reflected an AE were also recorded on the Adverse Event Form. However, changes in treatment of asthma were excepted, unless they met the AE definition as described above.

Signs (Clinical and Laboratory Findings): Any adverse finding judged by the investigator to be clinically significant was identified and commented upon in the CRF.

***SAEs*:** The investigator was instructed to immediately inform the Astra USA, Inc., monitor of any SAE that occurred during the study. In addition to entering each SAE on the CRF, the investigator was instructed to complete a separate Serious Adverse Event Form. The investigator was asked to assess all SAEs regarding causal relationship to the study drug according to the following classifications:

- **Probable**: A temporal relationship existed. No other possible causative factors(s) existed. Improvement on dechallenge or dose reduction (if performed) occurred. Recurrence of symptoms on rechallenge (if performed) occurred. A specific laboratory investigation (if performed) confirmed the relationship.
- **Possible**: A temporal relationship existed. Other possible causative factors(s) *may* have existed. Improvement on dechallenge or dose reduction may or may not have been seen.
- **Unlikely**: A temporal relationship was non-existent or doubtful and/or other factor(s) certain or probable to have been causative were not present.

Causality in cases where the disease had deteriorated due to lack of effect were classified as unlikely.

Unresolved Adverse Events: If an AE was present when the study was completed or terminated, its subsequent course was followed and reported to the Astra USA, Inc., monitor until the AE had resolved or until otherwise agreed.

8.1.3.7 Treatment and Measurement Discontinuation

[60:20]

Patients were free to discontinue their participation in the study at any time. The patient's participation in the study could have been discontinued at any time at the discretion of the investigator and/or sponsor. Examples of justifiable reasons to discontinue a patient from the study included the following:

- worsening of airways symptoms, becoming intolerable or resulting in unacceptable risks to the patient, and/or requiring the use of non-permitted asthma medications, and/or hospitalization (treatment failure);
- occurrence or worsening of intolerable AEs and/or other diseases including hospitalization;
- development of an exclusion criterion;
- patient or guardian became uncooperative;

- erroneous inclusion in the study;
- termination of the study by the sponsor.

Patients who discontinued their participation in the study were contacted by the investigator to obtain information about the reasons for the discontinuation, any possible AEs, and retrieval of study drug. Whenever possible, the patient was asked to return to the clinic for final clinical evaluations. If a patient discontinued participation from the study due to asthma symptoms, the reasons for discontinuation were reported on the Study Termination Form. If there were reasonable possibilities that the symptoms were not consistent with the natural history of the patient's disease, or that the symptoms could have been caused by the study drug, as judged by the investigator, the reasons for discontinuation were to be reported as an adverse event.

8.1.3.8 Statistical Analysis

[60:34-40]

8.1.3.8.1 Analytical Plan

The All Patients Treated (APT) approach was the main efficacy analysis for this study. It included all the patients who received at least one dose of study drug after the baseline phase, and had at least one observation taken while receiving study drug. For safety analyses, all randomized patients were included.

For the primary efficacy endpoints, a Per Protocol analysis (which included data from all patients included in the APT approach but who were not considered to be major protocol violators) was also performed.

Data to be excluded at all time points for a per protocol analysis - for events up to randomization:

- Age less than 12 weeks or greater than ten years.
- Primary diagnosis other than asthma.
- Use of short term (<14 days of use) steroids (except dermatological, nasal or inhaled) within 14 days of Visit 1, use of long term (≥14 days use) steroids (except dermatological, nasal or inhaled) within 42 days of Visit 1, use of long acting β_2-agonists within 48 hours of Visit 1.
- Baseline FEV_1 less than 40% of predicted at Visit 1 or Visit 2 (unless the other value is >50% of predicted).
- Reversibility less than 12% at Visit 1 or Visit 2.
- Asthma symptoms on less than four of the seven days prior to randomization.

Partial exclusions, for a per protocol analysis - for events after randomization:

- Use of any steroids (except dermatological or nasal) other than study treatment. All data recorded after the first use of the steroid until 14 days after use were excluded.
- Use of long acting β_2-agonists. All data recorded after the first use until 48 hours after the last use were excluded.

- Compliance was only considered for exclusion from a per protocol analysis if there was documented evidence in the form of a letter from the investigator expressing a concern that the patient was non-compliant with respect to study drug.

A similar population to the Per Protocol Population was studied with the exception that for those patients who used steroids, data were only used up to the point of steroid use. Thereafter, a Last Value Carried Forward Approach was employed as if data were missing.

8.1.3.8.2 Handling of Dropouts

For the primary analysis (APT), summary data for patients who terminated the study early or missed study visits (and consequently had missing data) were carried forward and included in subsequent analysis. Baseline data were not carried forward. In order to investigate the possible effects that may be introduced by carrying data forward to subsequent time points, summarization of the primary efficacy endpoints (no hypothesis testing was performed) were provided for data that were not carried forward, i.e., only values present at a particular time point contributed to the analysis at that time point.

8.1.3.8.3 Statistical Methods

All statistical comparisons were carried out as two-sided tests. Probability values were rounded to three decimal places. Statistical significance was declared if the p-value was less than or equal to 0.050. Statistical significance of interactions was tested at the 0.100 level of significance. The All Patients Treated Approach with the Last Value Carried Forward is presented in the main body of this report.

8.1.3.8.3.1 Statistical Methods: Efficacy Variables

8.1.3.8.3.1.1 Primary Efficacy Variables - Nighttime And Daytime Asthma Symptom Scores

Summary statistics (means; mean changes; standard deviations of changes; 95% confidence intervals on the differences between the active treatment groups and placebo) were calculated for the change from the baseline measurement (mean of the last seven days prior to randomization) to the double-blind phase measurement (mean over 12 weeks, Weeks 0-12) for all treatment groups. Changes from baseline to the double-blind phase for the budesonide treatment groups compared to placebo were analyzed using analysis of variance techniques. Because only comparisons between placebo and each budesonide group were made, Dunnett-type adjustment procedure was chosen for multiplicity for the Week 0-12 analysis of nighttime and daytime asthma symptom scores.

Time to onset of action was also presented where onset was determined to be the first day that a statistically significant difference was achieved between the active treatment groups versus placebo for mean changes in nighttime and daytime asthma symptom scores from baseline.

Symptom scores were summarized (no hypothesis testing) according to baseline symptom severity categories. These categories were as follows:

Mild - average baseline score less than or equal to 1.
Moderate - average baseline score greater than 1 and less or equal to 2.
Severe - average baseline score greater than 2.

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

The budesonide treatment groups were compared to placebo (Fisher's Exact Test) for the proportions of patients that were discontinued from double-blind treatment and classified as treatment failures. Changes from baseline to double-blind treatment in the numbers of days or the amount of breakthrough medication used were summarized for those patients who did not switch from their official study-designated breakthrough medication.

8.1.3.8.3.1.3 Secondary Efficacy Variables - FEV_1, FVC, $FEF_{25-75\%}$, Evening and Morning PEFs (in the subpopulation of patients who were able to perform the tests correctly)

FEV_1, FVC with its corresponding $FEF_{25-75\%}$, evening and morning PEFs were analyzed using analysis of variance techniques.

8.1.3.8.3.2 Statistical Methods: Safety Variables

Analysis of AEs and all other safety variables were performed for all randomized subjects. The incidence of clinical AEs, discontinuations due to AEs, drug-related, serious and severe AEs were summarized during the active treatment phase.

Differences between the budesonide treatment groups compared to placebo with respect to changes in the response of cortisol to ACTH stimulation from baseline to the double-blind phase were assessed using ANOVA techniques. In addition, numbers (%) of patients with HPA-axis suppression were also summarized for the double-blind treatment phase. A patient was said to have HPA-axis suppression when the following definition of normal HPA-axis function for the last on-therapy set of double-blind values was not met:

- A basal (i.e., pre-ACTH stimulation) value of at least 150 nmol/L,
- An ACTH-stimulated value of at least 400 nmol/L or an increase (stimulated - basal) of at least 200 nmol/L (or both).

Changes from baseline to double-blind treatment in clinical chemistry, hematology, urinalysis, physical examinations and vital signs were also summarized. In some instances, height measurements were made using uncalibrated stadiometers. These data were not included in the summaries. Summaries were provided for fungal culture data.

8.1.4 Results

8.1.4.1 Patient Disposition

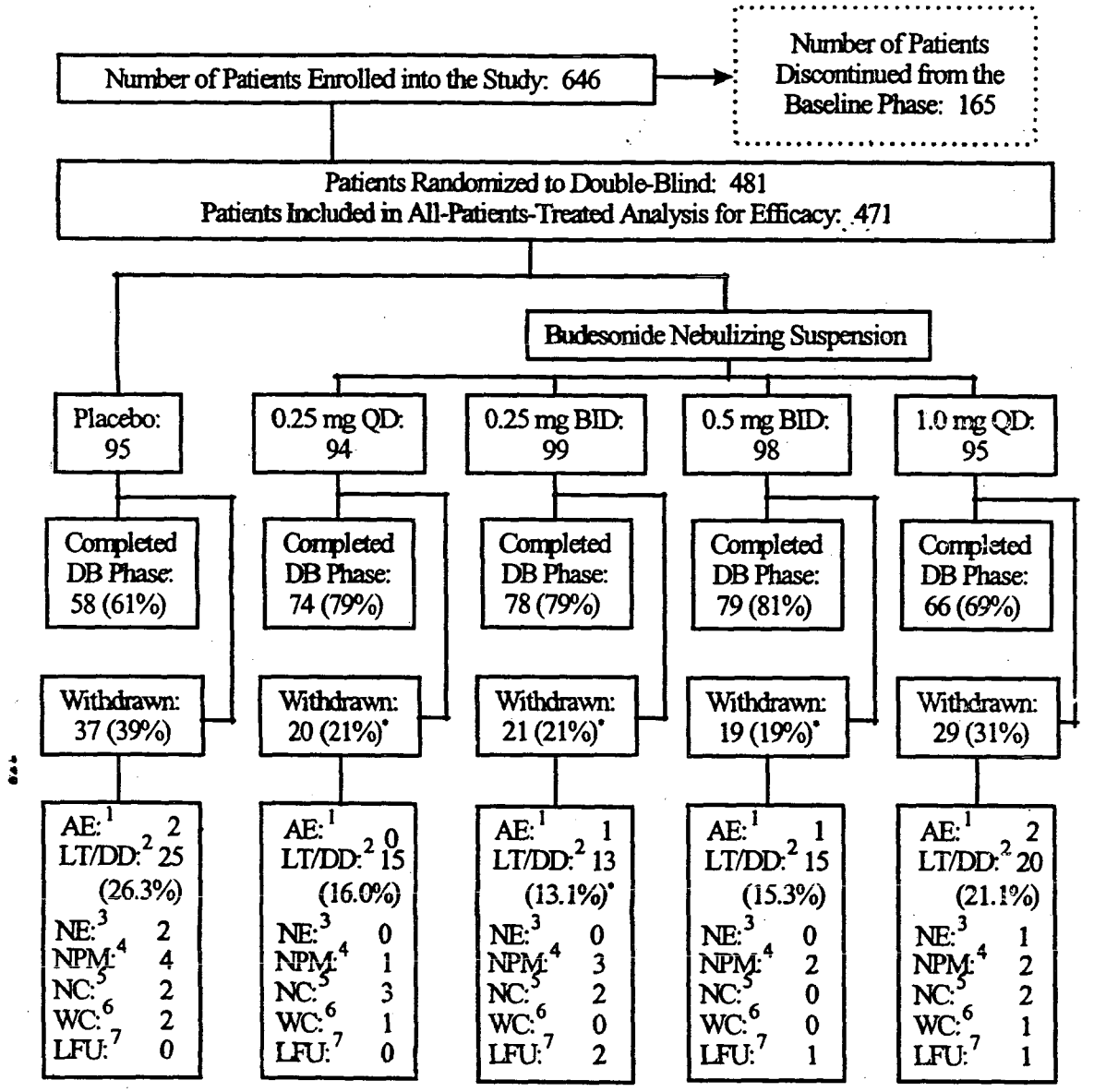
[60:41-4]
The first patient was enrolled into the study in May, 1995. The last patient completed the study in June, 1996. The disposition of patients enrolled into the study is summarized in Figure 8.1.4.1. [60:74-9]

165 patients were discontinued from the baseline phase, i.e., not randomized. The most frequent reason for patients discontinuing from the baseline phase was failure to fulfill the randomization criteria for asthma symptoms for at least 5 of the 7 days prior to randomization (33% of patients). [60:74-9]

A summary of patient disposition for all 481 randomized patients is presented in Table 8.1.4.1. A total of 126 patients were discontinued from the treatment phase of the study. The proportion of patients who were discontinued from the placebo group (39%) was greater than that for the budesonide groups (19-31%). The proportion of patients in the placebo group discontinuing due to worsening asthma (26.3%) was also greater than for the budesonide groups (13.1-21.1%).

The APT analysis was conducted on 471 patients. Ten randomized patients had no assessments made in the treatment phase and were excluded from the APT analysis. Of 481 patients randomized, 13 were judged to be completely non-evaluable for the Per Protocol analysis (10 of these were also excluded from the APT analysis) and 85 were partially evaluable. The most frequent reason for partial non-evaluability was "patient took short-term steroid." [60:91-4]

Figure 8.1.4.1. Disposition of Patients [60:42]



[1] AE = Adverse Event
[2] LT/DD = Lack of Therapeutic Effect/Disease Deterioration
[3] NE = Not Eligible
[4] NPM = Non-Protocol Use of Medication
[5] NC = Noncompliance with Study Procedures
[6] WC = Withdrew Consent
[7] LFU = Lost to Follow-up
* $p<0.05$ versus placebo

Table 8.1.4.1. Summary of Patient Disposition. [60:43]

Number of Patients	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Randomized	95	94	99	98	95
Completed Double-Blind Treatment	58 (61%)	74 (79%)	78 (79%)	79 (81%)	66 (69%)
Total No. Patients Discontinued:	37 (39%)	20 (21%)*	21 (21%)**	19 (19%)**	29 (31%)
Worsening Asthma[1]	25 (26.3%)	15 (16.0%)	13 (13.1%)*	15 (15.3%)	20 (21.1%)
Adverse Event	2 (2%)	0 (0%)	1 (1%)	1 (1%)	2 (2%)
Use of Medication Excluded by Protocol[2]	4 (4.2%)	1 (1.1%)	3 (3%)	2 (2%)	2 (2.1%)
Not Eligible	2 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)
Non-Compliance w/Study Procedures	2 (2.1%)	3 (3.2%)	2 (2%)	0 (0%)	2 (2.1%)
Withdrew Consent	2 (2.1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Lost to Follow-up	0 (0%)	0 (0%)	2 (2%)	1 (1%)	1 (1%)
Evaluated for Efficacy Analyses APT/PP[3]	92/92	93/91	97/96	96/96	93/93
Evaluated for Safety	95	94	99	97[4]	95

[1] Includes patients who were discontinued due to lack of therapeutic effect or disease deterioration, and patients who received steroids for worsening asthma not permitted by the protocol.
[2] Steroid medications for indications other than worsening of asthma.
[3] Individual patient data were partially excluded from per protocol efficacy calculations for 24, 13, 12, 17 and 19 patients in the placebo, 0.25 mg QD, 0.25 mg BID, 0.5 mg BID and 1.0 mg QD groups, respectively.
[4] One randomized patient never took study drug, therefore was not included in the safety analysis.
Data Source: [Section 14.1.1, Tables 3 and 4; 60:80-5].
*$p \leq 0.050$ versus placebo.
**$p \leq 0.010$ versus placebo.

8.1.4.2 Demographic and Other Baseline Characteristics

[60:44-9]

The basic demographic characteristics of the study population are summarized in Table 8.1.4.2. The basic demographic characteristics were similar for the five treatment groups.

Reviewer's Comments: 1. Only 7 patients in this study were younger than 11 months old and 12 younger than one year old. These were less than the targeted enrollments (n=24 and 28, respectively). 2. The male to female ratio in this study is typical of asthma patients in this age group. 3. The number of Black (African-American) patients in the placebo group was less than that of budesonide groups. But, this would not lead to a predictable confounding effect. 4. The proportion of patients on inhaled corticosteroids prior to the randomization was highest in the placebo group. This might have led to an exaggerated treatment effect.

Table 8.1.4.2. Demographic characteristics. [60:45]

Variable	Placebo	Budesonide Nebulizing Suspension				
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD	Total
n	95	94	99	98	95	481
Gender: [1]						
Male	59 (62.1%)	59 (62.8%)	62 (62.6%)	68 (69.4%)	62 (65.3%)	310 (64.4%)
Female	36 (37.9%)	35 (37.2%)	37 (37.4%)	30 (30.6%)	33 (34.7%)	171 (35.6%)
Age (months): [1]						
Mean±SD	57.8±26.1	54.6±25.3	54.3±26.8	53.0±26.2	55.6±27.2	55.0±26.3
Range	11-100	8-107	7-105	9-107	8-108	7-108
Race: [1]						
Caucasian	82 (86.3%)	72 (76.6%)	75 (75.8%)	82 (83.7%)	76 (80.0%)	387 (80.5%)
Black	7 (7.4%)	18 (19.1%)	19 (19.2%)	11 (11.2%)	11 (11.6%)	66 (13.7%)
Hispanic	4 (4.2%)	3 (3.2%)	3 (3.0%)	3 (3.1%)	5 (5.3%)	18 (3.7%)
Oriental	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	2 (0.4%)
Other	1 (1.1%)	1 (1.1%)	2 (2.0%)	2 (2.0%)	2 (2.1%)	8 (1.7%)
Weight (Mean±SD): [1]						
Pounds	43.5±14.0	44.1±20.0	42.4±15.2	43.6±18.2	42.0±13.8	43.1±16.3
Kilograms	19.7±6.4	20.0±9.0	19.2±6.9	19.8±8.2	19.0±6.3	19.5±7.4
Height (cm): [1]						
Mean±SD	107.9±15.4	107.0±16.6	105.0±17.0	105.9±16.6	106.7±16.7	106.5±16.4
Patients on Inhaled Corticosteroids: [2]						
Beclomethasone	24 (25%)	17 (18%)	16 (16%)	20 (20%)	22 (23%)	99 (21%)
Triamcinolone	13 (14%)	7 (7%)	13 (13%)	13 (13%)	11 (12%)	57 (12%)
Flunisolide	8 (8%)	8 (9%)	7 (7%)	6 (6%)	6 (6%)	35 (7%)

[1] Source: [Section 14.1.2, Table 1; 60:96-9]
[2] Source: [Section 14.1.2, Table 6; 60:107-8] WHO highest level name; numbers are not mutually exclusive.

8.1.4.2.1 Baseline Asthma Symptom Scores and Pulmonary Function Test Data

[60:45-7, 96-9]

The mean duration of asthma at entry into the study, the baseline asthma symptom scores, FEV_1, and PEFs are summarized in Table 8.1.4.2.1 There were no statistical differences at baseline between the treatment groups for any of these variables.

Table 8.1.4.2.1. Baseline lung function and asthma symptom scores. [60:47]

Variable	Placebo	Budesonide Nebulizing Suspension				
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD	Total
n	95	94	99	98	95	481
Duration of Asthma (months)						
Mean±SD	35.6±22.9	34.2±22.8	32.4±22.9	33.3±22.7	35.4±23.9	34.2±22.9
Range	5-90	2-92	4-96	4-88	6-98	2-98
Nighttime Asthma Symptom Scores:						
Mean±SD	1.16±0.64	1.13±0.57	1.33±0.64	1.20±0.62	1.25±0.63	1.22±0.62
Daytime Asthma Symptom Scores:						
Mean±SD	1.27±0.49	1.21±0.45	1.31±0.49	1.33±0.52	1.28±0.57	1.28±0.50
PFT Able:						
Yes	32 (33.7%)	33 (35.1%)	34 (34.3%)	30 (30.6%)	35 (36.8%)	164 (34.1%)
No	63 (66.3%)	61 (64.9%)	65 (65.7%)	68 (69.4%)	60 (63.2%)	317 (65.9%)
FEV_1 (L):	1.17±0.29	1.16±0.32	1.20±0.33	1.22±0.35	1.14±0.28	1.18±0.31
(n)	(31)	(33)	(34)	(30)	(35)	(163)
% Predicted	79.1±17.1	78.7±16.7	83.1±20.4	79.8±20.9	78.3±14.4	79.8±17.8
(n)	(32)	(33)	(34)	(30)	(36)	(165)
% Reversibility	29.1±18.1	28.9±15.4	30.5±16.6	30.5±19.0	26.9±11.8	29.1±16.1
Morning PEF (L/min):						
(n)	(32)	(32)	(34)	(29)	(34)	(161)
Mean±SD	155.8±37.9	164.2±53.8	157.1±33.6	166.9±48.8	156.6±40.6	159.9±43.0
Evening PEF (L/min):						
(n)	(32)	(32)	(34)	(29)	(34)	(161)
Mean±SD	160.8±37.1	169.9±51.7	168.7±36.5	176.7±53.5	166.2±36.2	168.3±43.1

Data Source: [Section 14.1.2, Table 1; 60:96-9]

8.1.4.2.2 *Baseline Physical Examination, Previous and Concomitant Diseases*

[60:47-8, 100-5]

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

The treatment groups were similar with respect to diagnoses, which were present at baseline in addition to asthma and with frequencies ≥1%. Approximately half of the patients had allergic rhinitis. Dermatitis, chronic sinusitis, otitis media, headache, rhinitis due to pollen, chronic rhinitis, and nasal and sinus disease not elsewhere classified, were

represented in 6-14% of patients. Other concomitant diseases were present in fewer than 6% of the patients. The most frequently reported past diagnosis was otitis media (36%).

8.1.4.2.3 Prior and Concomitant Medications

[60:48-9]

8.1.4.2.3.1 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 and/or inhaled salbutamol; ≥99%), cromoglicic acid (cromolyn sodium; 72%), prednisolone (27%); beclomethasone (21%), triamcinolone (12%) and theophylline (10%). [60:106-8]

Concomitant asthma medications: All patients used β_2-agonists at some time during the double-blind treatment phase. Eighteen percent of the patients used parenteral/oral steroids at some time during the study, and about 9% received other antiinflammatory agents. [Amendment 2/5/98: Protocol 04-3100, Section 14.1.2, Tables 7-8]

8.1.4.2.3.2 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 (57%), nasal preparations (51%), systemic antibacterials (35%), analgesics (26%), systemic antihistamines (17%), cough and cold preparations (13%), and vitamins (10%). [60:111-6]

Concomitant non-asthma medications: The use of concomitant non-asthma medications was similar among treatment groups. Drug classes mentioned most frequently were dermatologic preparations (50%), systemic antibacterials (46%), analgesics (36%), nasal preparations (27%), cough and cold preparations (18%), systemic antihistamines (11%), and antiinflammatory and antirheumatic products (10%). [60:117-22]

8.1.4.3 Measurements of Treatment Compliance

[60:49; 63:65]

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 96-98% of the patients for Week 2; 82-97% for Week 4; 76-93% for Week 8; and 68-85% for Week 12.

8.1.4.4 Efficacy Analysis

8.1.4.4.1 Primary Efficacy Variables

[60:49-55]

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

Table 8.1.4.4.1.1. Changes in asthma symptom scores; All Patients Treated, Last Value Carried Forward, Total Population.

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Asthma Symptom Score (scale of 0-3):[1]					
Mean Change from Baseline[2]					
n	92	93	97	96	93
Nighttime	-0.13	-0.28	-0.49	-0.42	-0.40
(p-value vs. placebo)		(0.121)	(<0.001)**	(0.003)**	(0.005)**
n	92	92	97	96	93
Daytime	-0.19	-0.28	-0.40	-0.46	-0.37
(p-value vs. placebo)		(0.337)	(0.019)**	(0.003)**	(0.047)*

[1] Data sources: [Section 14.2, Table 1; 60:124-9]
[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 0.25 mg BID, 0.5 mg BID and 1.0 mg QD budesonide groups were statistically significantly greater compared to placebo ($p \leq 0.005$), with a numerical improvement for the 0.25 mg QD group (p=0.121). When the Dunnett's adjustment was applied, the budesonide groups maintained their superiority over the placebo group. This is shown graphically in Figure 8.1.4.4.1.1A.

For daytime asthma symptom scores, the adjusted mean changes from baseline to Weeks 0-12 in patients of the 0.25 mg BID, 0.5 mg BID and 1.0 mg QD budesonide groups were statistically significantly greater compared to placebo ($p \leq 0.047$), with a numerical improvement for the 0.25 mg QD group (p=0.337). When the Dunnett's adjustment was applied, the 0.25 mg BID and 0.5 mg BID budesonide groups maintained superiority over the placebo group. This is shown graphically in Figure 8.1.4.4.1.1B.

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 was observed by Week 2 and was sustained throughout the 12-week double-blind treatment phase. This is shown graphically in Figure 8.1.4.4.1.1C and D. [60:124-5, 126-7]

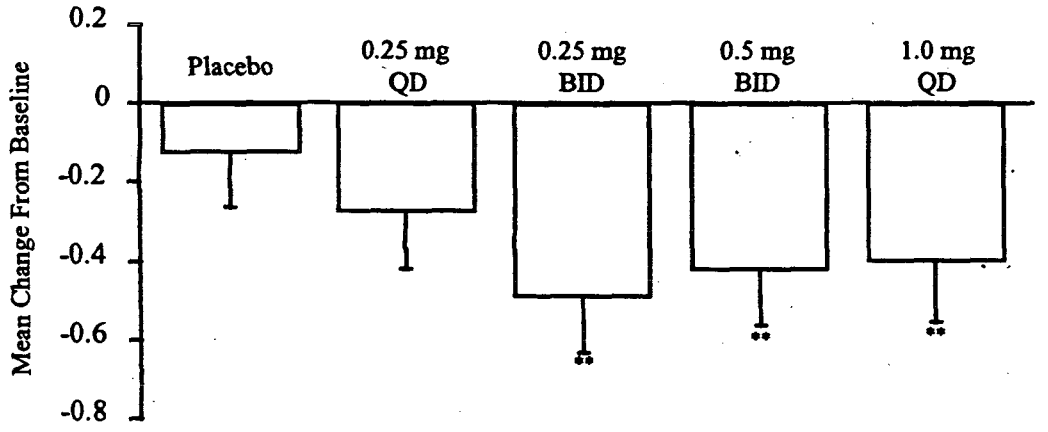
Reviewer's Comments: However, when comparing each individual budesonide group to placebo,

the statistically significant differences for daytime symptom scores in all three budesonide groups were not observed until Weeks 2-4. The statistically significant differences for nighttime symptom scores were observed in Weeks 0-2.

> 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 both nighttime and daytime asthma symptom scores between all budesonide treatment groups combined compared to placebo were observed on Day 2 ($p<0.050$). [Amendment 1/7/98; 60:144-51]

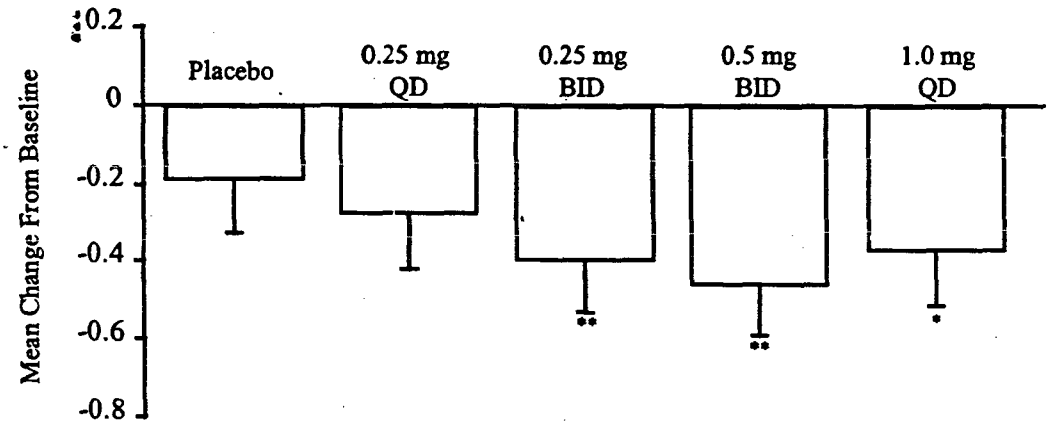
Reviewer's Comments: While the above separations from placebo were observed, the differences in changes of nighttime and daytime asthma symptom scores between the budesonide and placebo groups were not statistically significant in most of the first 14 days of treatment phase (except Days 2-3 and 8-10 for nighttime scores and Days 2 and 8-9 for daytime scores).

Figure 8.1.4.4.1.1A. 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.



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

Figure 8.1.4.4.1.1B. 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.



[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 8.1.4.4.1.1C. Summary of mean nighttime asthma symptom scores; All Patients Treated Analysis, Last Value Carried Forward, Total Population.

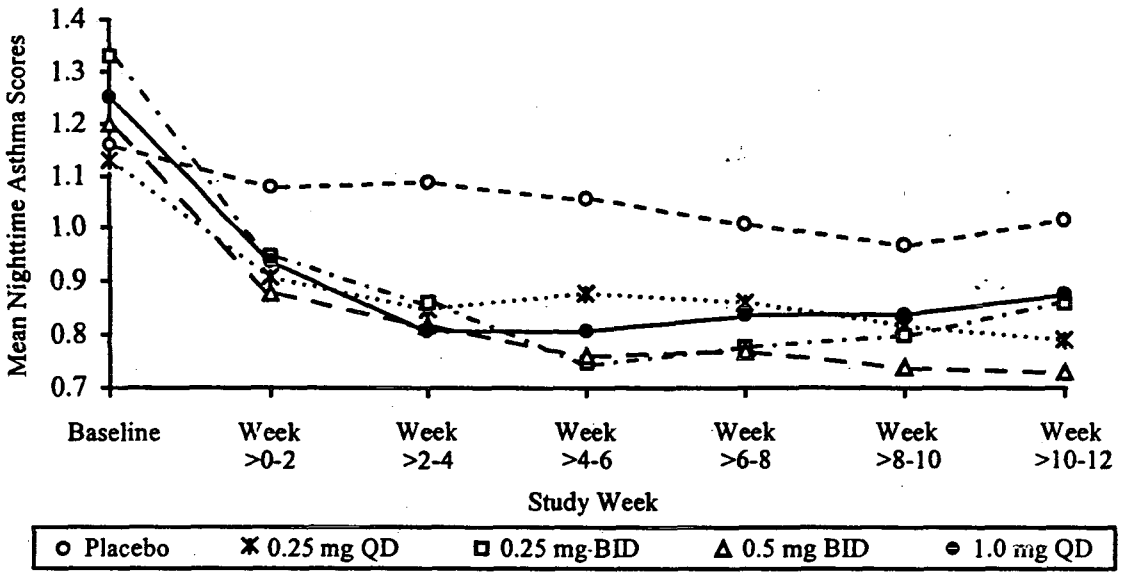
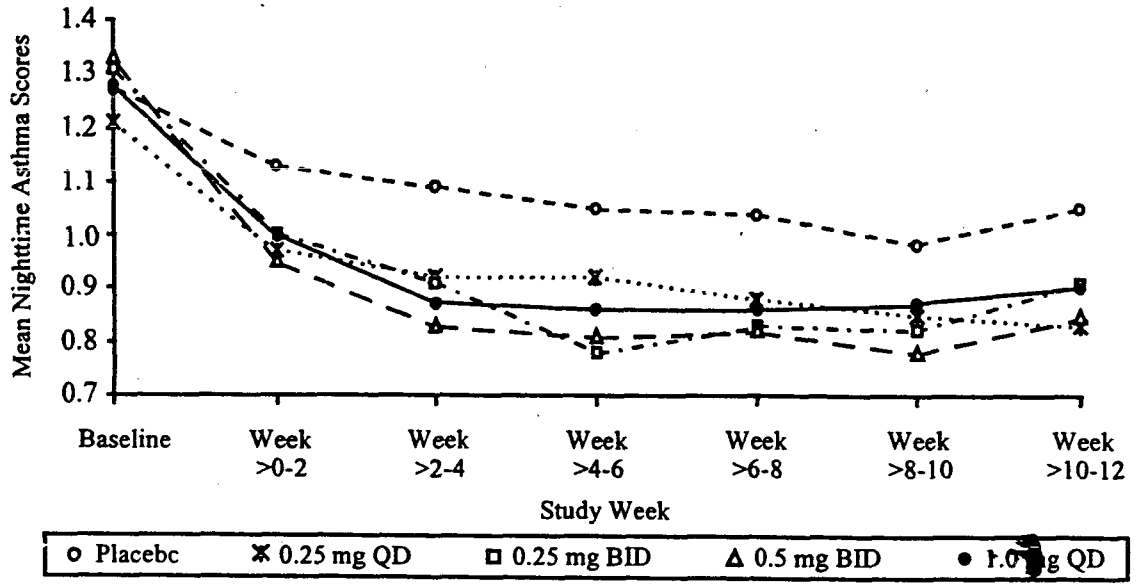


Figure 8.1.4.4.1.1D. Summary of mean daytime asthma symptom scores; All Patients Treated Analysis, Last Value Carried Forward, Total Population.



8.1.4.4.1.2 Nighttime and Daytime Asthma Symptom Scores, by Prior Inhaled Steroid Therapy; All Patients Treated, Last Value Carried Forward

A total of 145 (30.8%) of the patients were on inhaled steroids up to randomization. In general, the patients that were not on inhaled steroids up to randomization had greater improvements in nighttime and daytime asthma symptom scores compared to those patients who were previously on inhaled steroids; this even existed among the placebo groups. Patients that were previously on inhaled steroids and were randomized to 0.25 mg BID, 0.5 mg BID and 1.0 mg QD budesonide nebulizing suspension showed improvements in nighttime and daytime asthma symptom scores compared to those patients that were on inhaled steroids and randomized to placebo. [60:154-5]

Reviewer's Comments: The proportion of patients on inhaled steroids prior to the randomization was highest in the placebo group (Table 8.1.4.2). This might have led to an exaggerated treatment effect since patients who were not on inhaled steroids prior to randomization (more in the budesonide groups) had greater improvements in asthma symptom scores compared to those patients who were previously on inhaled steroids (more in the placebo group).

8.1.4.4.1.3 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. [60:156-7]

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

A total of 208 (44.2%) patients were classified into the 0-4 years age group. For the breakdown by age classification (i.e., 0-4 years; >4 years), the differences between the active and placebo treatment groups remained. There were no apparent differences between the age categories for any of the treatment groups. [60:154-5]

8.1.4.4.1.5 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. [60:159-60]

For nighttime asthma symptom scores, 33-48% of the patients treated with budesonide were classified as improved by at least 0.5 points compared to 28% for placebo. Three to 8% of the patients on budesonide were classified as worsened by at least 0.5 points compared to 14% for placebo. Forty-six to 61% of the patients on budesonide were classified as having no change (-0.5 points < change < 0.5 points) compared to 58% for placebo.

For daytime asthma symptom scores, 29 to 51% of the patients treated with budesonide

showed improvement of at least 0.5 points compared to 32% for placebo. Three to 9% of the patients on budesonide were classified as worsened, compared to 12% for placebo. Forty-six to 65% of the patients on budesonide were classified as having no change (-0.5 points < change < 0.5 points) compared to 57% 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 (60% for nighttime scores and 61% for daytime scores).

8.1.4.4.1.6 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 analysis. [60:152-3]

Reviewer's Comments: However, the adjusted mean change from baseline to Weeks 0-12 for daytime asthma symptom scores of patients in the 1.0 mg QD budesonide group was not significantly different from that of placebo by per protocol analysis.

8.1.4.4.2 Secondary Efficacy Variables

[60:56-8]

8.1.4.4.2.1 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 ($p \leq 0.014$).

Table 8.1.4.4.2.1A. Number of days use of breakthrough medication; All Patients Treated, Last Value Carried Forward, Total Population.

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Use of Breakthrough Medication[1]					
n	92	93	97	96	93
Baseline	7.26	8.73	9.01	8.10	8.35
Mean Change from Baseline[2]	-2.36	-4.39	-5.22	-4.92	-4.38
(p-value vs. placebo)		(0.013)*	(<0.001)*	(0.002)*	(0.014)*

[1] Data source: [Section 14.2, Table 15; 60:162]
[2] Mean change adjusted for center effect.
* Statistically significantly different from placebo at the .05 level.

Patients on budesonide used less amount of breakthrough medication (as the number of puffs or nebulizations of breakthrough medication used per day) than placebo.

Table 8.1.4.4.2.1B. Amount of breakthrough medication used; All Patients Treated, Last Value Carried Forward, Total Population. [60:163]

Variable (Weeks 1-12)	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Use of nebulizer					
n	57	55	63	70	64
Baseline[1]	1.19	1.04	1.28	1.44	1.32
Mean Change from Baseline[1]	-0.03	-0.40	-0.69	-0.87	-0.60
Use of pMDI					
n	21	22	24	18	20
Baseline[1]	1.93	2.84	2.59	1.67	2.04
Mean Change from Baseline[1]	-0.36	-1.65	-1.63	-0.94	-0.71

[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.

8.1.4.4.2.2 Proportion of Patient Discontinuations from the Study

See Section 8.1.4.1.

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

Of the morning PEF, there were statistically significant improvements in the 0.25 mg BID, 0.5 mg BID and 1.0 mg QD budesonide treatment groups compared to placebo. There were numerical improvements in the 0.25 mg QD budesonide treatment group compared to placebo.

Of the evening PEF, there were statistically significant improvements in the 0.25 mg QD, 0.25 mg BID, and 0.5 mg BID budesonide treatment groups compared to placebo. There were numerical improvements in the 1.0 mg QD budesonide treatment groups compared to placebo.

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

Table 8.1.4.4.2.3. Mean changes from baseline in morning and Evening PEFs; All Patients Treated, Last Value Carried Forward, Subgroup of Total Population that could perform the maneuvers. [60:165, 170]

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
PEF[1]: n	32	32	34	29	34
Mean Change from Baseline (L/min)[2]					
Morning	-0.2	10.9	23.0	24.8	17.1
(p-value vs. placebo)		(0.165)	(0.003)*	(0.004)*	(0.030)*
Evening	1.9	16.8	19.2	21.0	14.1
(p-value vs. placebo)		(0.034)*	(0.012)*	(0.010)*	(0.078)

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

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

There were numerical improvements in FEV_1, FVC and $FEF_{25-75\%}$ in the budesonide groups compared to placebo. Except FEV_1 and FVC for the 0.5 mg BID budesonide group, these improvements were not significantly different.

Table 8.1.4.4.2.4. 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. [60:166-70]

Variable (Weeks 0-12)	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Spirometry[1]: n	28	31	33	29	34
Mean Change from Baseline [2]					
FEV_1 (L)	0.04	0.07	0.08	0.17	0.11
(p-value vs. placebo)		(0.606)	(0.405)	(0.031)*	(0.178)
FVC (L)	0.00	0.09	0.10	0.20	0.08
(p-value vs. placebo)		(0.158)	(0.101)	(0.003)*	(0.193)
$FEF_{25-75\%}$ (L/sec)	0.07	0.10	0.08	0.23	0.20
(p-value vs. placebo)		(0.732)	(0.869)	(0.10[illegible])	(0.175)

[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.

8.1.4.5 Safety Analysis

[60:60-71]

8.1.4.5.1 Extent of Exposure

The mean number of days exposure to study drug for the patients randomized to the budesonide groups was higher compared to placebo.

Table 8.1.4.5.1. Exposure to study drug (days) [60:60]

Statistic	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
n	95	94	99	97[1]	95
Mean	62	75	75	77	68
Median	83	84	84	84	84
SD	32	21	23	19	27
Range	1-98	1-93	1-93	1-92	1-92

[1]Patient 41-0783 did not take any study drug, therefore was not included in the safety analysis.

8.1.4.5.2 Adverse Events

[60:60-67]

8.1.4.5.2.1 Brief Summary of Adverse Events

There were no deaths reported during the study.

During the baseline phase: There were a total of five SAEs in four patients who were not randomized into the treatment phase of the study (Table 8.1.4.5.2.4). The overall incidence of AEs was 35% for patients that were subsequently randomized to the budesonide groups compared to 39% for patients that were subsequently randomized to the placebo group. [60: 200]

During the treatment phase: A total of 15 SAEs in 13 patients were reported (Table 8.1.4.5.2.4). One of the SAEs (laryngismus) leading to discontinuation from the treatment phase was judged by the investigator to be of probable relationship to study treatment. A total of six patients were discontinued from the treatment phase due to AEs (Table 8.1.4.5.2.5).

The number of AEs was similar for the placebo and four budesonide groups (77% of the patients in the placebo group; 81% of the patients in the budesonide groups). [60:203] The commonly reported AEs (≥5% of patients in any treatment group) were similar between the placebo and the budesonide groups, with a higher incidence of respiratory infections in the budesonide groups with the highest dose regimens, i.e., 0.5 mg BID or 1 mg QD (Table 8.1.4.5.2.2). Except respiratory infections, there were no apparent budesonide dose effects in the incidence of AEs overall.

8.1.4.5.2.2 Display of All Adverse Events

The commonly reported AEs in ≥5% of patients in any treatment group are summarized in Table 8.1.4.5.2.2.

Table 8.1.4.5.2.2. Summary of most frequently reported AEs (≥5% of patients in any one budesonide treatment group) during the treatment phase[1].

Body System/AE	Placebo	Budesonide Nebulizing Suspension				
		0.25 mg QD	0.25mg BID	0.5 mg BID	1.0 mg QD	Total
n	95	94	99	97	95	385
Respiratory System Disorders						
Respiratory Infection	28 (29%)	30 (32%)	30 (30%)	40 (41%)	36 (38%)	136 (35%)
Sinusitis	19 (20%)	15 (16%)	10 (10%)	15 (15%)	15 (16%)	55 (14%)
Rhinitis	9 (9%)	9 (10%)	9 (9%)	13 (13%)	8 (8%)	39 (10%)
Coughing	7 (7%)	5 (5%)	6 (6%)	7 (7%)	5 (5%)	23 (6%)
Bronchospasm	9 (9%)	5 (5%)	4 (4%)	4 (4%)	2 (2%)	15 (4%)
Pharyngitis	5 (5%)	3 (3%)	6 (6%)	3 (3%)	3 (3%)	15 (4%)
Bronchitis	7 (7%)	1 (1%)	5 (5%)	4 (4%)	2 (2%)	12 (3%)
Body as a Whole						
Fever	19 (20%)	19 (20%)	17 (17%)	16 (16%)	18 (19%)	70 (18%)
Accident and/or Injury	7 (7%)	6 (6%)	8 (8%)	9 (9%)	6 (6%)	29 (8%)
Pain	-	1 (1%)	1 (1%)	3 (3%)	5 (5%)	10 (3%)
Resistance Mechanism Disorders						
Otitis Media	15 (16%)	14 (15%)	14 (14%)	10 (10%)	11 (12%)	49 (13%)
Infection Viral	3 (3%)	5 (5%)	6 (6%)	3 (3%)	4 (4%)	18 (5%)
Moniliasis	2 (2%)	6 (6%)	4 (4%)	2 (2%)	6 (6%)	18 (5%)
Gastrointestinal System Disorders						
Gastroenteritis	6 (6%)	6 (6%)	7 (7%)	7 (7%)	3 (3%)	23 (6%)
Vomiting	2 (2%)	2 (2%)	6 (6%)	5 (5%)	2 (2%)	15 (4%)
Central & Peripheral Nervous System Disorder						
Headache	8 (8%)	3 (3%)	5 (5%)	5 (5%)	6 (6%)	19 (5%)
Hearing & Vestibular Disorders						
Ear Infection NOS	3 (3%)	2 (2%)	4 (4%)	6 (6%)	6 (6%)	18 (5%)

[1]Data source: [60: 203-8]

Reviewer's Comments: In AEs with ≥5% or <5% of patients in any budesonide group, there was no apparent difference between the placebo and the budesonide groups.

8.1.4.5.2.3 Analysis of Adverse Events

The incidences of adverse events considered by the investigator to be possibly or probably related to treatment were similar between the placebo and the budesonide groups. The incidence of moniliasis was higher in 0.25 mg or 1.0 mg QD budesonide treatment groups compared to placebo (5, 6, and 2%, respectively). [60:209-210]

8.1.4.5.2.4 Serious Adverse Events

There were no deaths reported during this study. Table 8.1.4.5.2.4 summarizes the SAEs reported during the baseline and treatment phases. A total of 20 SAEs in 17 patients were reported. Five SAEs in four patients were reported during baseline; these patients were not randomized into the study. Fifteen SAEs in 13 patients were reported during the treatment phase. In one case, who was on budesonide 1.0 mg QD, the investigator judged the SAE (laryngismus) to be probably related to study treatment. All events resolved without sequelae.

Table 8.1.4.5.2.4. Summary of serious adverse events[1].

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Baseline:		
18-E009	Bronchospasm occurring during baseline treatment.	N/A
21-E006	Bronchospasm occurring during baseline treatment.	N/A
	Pneumonia occurring during baseline treatment.	N/A
33-E013	Bronchospasm occurring during baseline treatment.	N/A
35-E007	Bronchospasm occurring during baseline treatment.	N/A
Placebo:		
14-0753	Bronchospasm/completely recovered.	Unlikely
22-0391	Pneumonia lobar/completely recovered.	Unlikely
23-0510	Bronchospasm/completely recovered.	Unlikely
31-0586	Bronchospasm/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 0.25 mg QD:		
13-0342	Otitis media/completely recovered.	Unlikely
	Ear infection external/completely recovered.	Unlikely
13-0349	Bronchospasm/completely recovered.	Unlikely
29-0550	Bronchospasm/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 0.25 mg BID:		
25-0251	Bronchospasm/completely recovered.	Unlikely
	Pneumonia/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 0.5 mg BID:		
33-0569	Bronchospasm/completely recovered.	Unlikely
Budesonide Nebulizing Suspension 1.0 mg QD:		
10-0162	Pneumonia/completely recovered.	Unlikely
14-0219	Accident and/or injury/completely recovered.	Unlikely
14-0626	Bronchospasm/completely recovered.	Unlikely
20-0479	Laryngismus/completely recovered.	Probable

[1] Data sources: [60:213, 222-30]
[2] WHO preferred term.

8.1.4.5.2.5 Discontinuations Due to Adverse Events

Table 8.1.4.5.2.5 summarizes the discontinuations due to adverse events. During the baseline phase, one discontinuation was reported; the patient was not randomized into the study. During the treatment phase, a total of 6 discontinuations were reported. All events eventually resolved without sequelae.

Table 8.1.4.5.2.5. Summary of discontinuations due to adverse events.[1]

Patient Number	Adverse Event[2]	Causality: Investigator's Assessment
Baseline:		
18-E009	Bronchospasm occurring during baseline treatment	N/A
Placebo:		
10-0164	Varicella/completely recovered.[3]	Unlikely
11-0179	Bronchospasm/completely recovered.[3]	Unlikely
Budesonide Nebulizing Suspension 0.25 mg BID:		
25-0251	Bronchospasm/completely recovered.[3] Pneumonia/completely recovered.[3]	Unlikely Unlikely
Budesonide Nebulizing Suspension 0.5 mg BID:		
11-0184	Bronchospasm/completely recovered.[3]	Unlikely
Budesonide Nebulizing Suspension 1.0 mg QD:		
17-0592	Respiratory infection/completely recovered.[3]	Unlikely
20-0479	Laryngismus/completely recovered.[3]	Probable

[1] Data sources: [60:220-30]
[2] WHO preferred term.
[3] As confirmed by the investigators following the patient's discontinuation from the study.

8.1.4.5.2.6 Adverse Events of Severe Intensity

[60:214-219]

Eight patients experienced AEs of severe intensity in the placebo group and 10, 12, 7 and 7 patients each, in the 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD budesonide groups, respectively. Bronchospasm was the most frequent severe AE with incidences of 6% in the placebo group and 2% in the total budesonide treatment group. Respiratory infection occurred in 2% of the budesonide-treated patients compared to 1% of the placebo patients. Otitis media occurred in 2% of all patients on budesonide compared to 0% in patients on placebo. All other severe AEs were reported with incidences of ≤1%.

8.1.4.5.3 Assessment of HPA-Axis

[60:69-71]

There were no consistent differences between the placebo and any budesonide group in test values that clearly indicated a HPA-axis suppression (Table 8.1.4.5.3A). 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 8.1.4.5.3B).

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 QD budesonide group (-44.1 nmol/L) compared to placebo (-28.1 nmol/L). The significance of this finding is uncertain but may suggest a measurable systemic effect of nebulized budesonide.

Table 8.1.4.5.3A. Summary results of ACTH-simulated cortisol tests.[1]

Variable			Placebo	Budesonide Nebulizing Suspension			
				0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
ACTH-Stimulated Cortisol Levels (nmol/L)							
	Basal	n	27	30	30	28	22
	ACTH-Stimulated	n	27	32	27	28	23
Basal:	Baseline		327	280	340	306	253
	Week 12		299	293	317	293	318
ACTH-Stimulated:	Baseline		686	634	661	650	644
	Week 12		644	643	629	638	592
Adjusted Mean Change in ACTH-Stimulated Corticol Levels from Baseline[2]			-28.1	26.2	-25.4	1.0	-44.1
	(p-value vs. placebo)			(0.158)	(0.946)	(0.468)	(0.703)

[1] Data source: [60:289]
[2] Means adjusted for Center Effect.

Table 8.1.4.5.3B. Shifts in ACTH stimulation test from baseline to double-blind treatment phase (Week 12).[1,2]

Para-meter	Base-line	Placebo n=27		Budesonide Nebulizing Suspension 0.25 mg QD n=30		0.25 mg BID n=27		0.5mg BID n=28		1.0 mg QD n=22	
		abn	norm	abn	norm	abn	norm	abn	norm	abn	norm
ACTH stim.	abn	-	2	-	1	-	4	1	1	1	2
Test[3]	norm	3	22	4	25	3	20	3	23	2	17

[1] Data source: [60:290]
[2] 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.

8.1.4.5.4 *Evaluation of Clinical Laboratory Tests*

[60:67-9]

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 the study treatment and due to concomitant diseases such as allergic rhinitis and viral/bacterial infections or hemolyzed/contaminated samples. In a few cases an explanation could not be found. [60:232--75]

8.1.4.5.5 *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.
[60:277-88]

8.1.4.5.6 *Assessment Of Oral And Nasal Fungal Cultures*

There were no apparent differences between treatment groups in clinically significant changes in fungal cultures. [60:294-6]

8.1.5 *Conclusions and Comments of Study Results*

This study of budesonide nebulizing suspension once or twice a day was performed in infants and young children aged six months to eight years who could have been using inhaled corticosteroids prior to randomization for the control of their asthma symptoms.

The results demonstrated that budesonide nebulizing suspension improved both primary and secondary efficacy variables compared to placebo (Table 8.1.5). The 0.25 mg QD regimen did not show a statistically significant improvement in most primary or secondary efficacy variables although it did show numerical improvement in several variables. The minimal efficacious dose was 0.25 mg BID. The 0.5 mg BID regimen achieved the most consistent efficacy, followed by 0.25 mg BID and 1.0 mg QD. After adjusting for multiple comparisons using Dunnett's test, only 0.25 mg BID and 0.5 mg BID regimens demonstrated significant improvement in both primary efficacy variables, i.e., nighttime and daytime asthma symptom scores; the 1.0 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 BID regimen demonstrated significant improvements in morning and evening PEFs, FEV_1, and FVC. So did the 0.25 mg BID regimen on morning and evening PEFs and the 1.0 mg QD regimen on morning PEF. All four budesonide regimens significantly decreased the use of breakthrough medication (short-acting inhaled bronchodilator). Only 1.0 mg QD budesonide regimen failed to demonstrate a statistically significant reduction in the

proportion of patients who discontinued from the study. It appears that the BID regimens were more efficacious than the QD regimens.

The safety evaluations did not reveal apparent difference between the treatment groups in reported adverse events, response to ACTH-stimulation tests, and changes in physical examinations or clinical laboratory tests.

Of note, only 7 patients in this study were younger than 11 month old and 12 younger than one year old. These were less than the targeted enrollments (n=24 and 28, respectively).

Table 8.1.5. Mean changes from baseline in primary and secondary efficacy variables; All Patients Treated, Last Value Carried Forward.[1]

Variable (Weeks 0-12) Mean Change from Baseline[2]	Placebo	Budesonide Nebulizing Suspension			
		0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Asthma Symptom Score (scale of 0-3):					
Nighttime	-0.13	-0.28	-0.49	-0.42	-0.40
(p-value vs. placebo)		(0.121)	(<0.001)**	(0.003)**	(0.005)**
Daytime	-0.19	-0.28	-0.40	-0.46	-0.37
(p-value vs. placebo)		(0.337)	(0.019)**	(0.003)**	(0.047)*
Use of Breakthrough Medication (days)	-2.36	-4.39	-5.22	-4.92	-4.38
(p-value vs. placebo)		(0.013)*	(<0.001)*	(0.002)*	(0.014)*
PEF (L/min)[3]:					
Morning	-0.2	10.9	23.0	24.8	17.1
(p-value vs. placebo)		(0.165)	(0.003)*	(0.004)*	(0.030)*
Evening	1.9	16.8	19.2	21.0	14.1
(p-value vs. placebo)		(0.034)	(0.012)*	(0.010)*	(0.078)
Spirometry[3]:					
FEV_1 (L)	0.04	0.07	0.08	0.17	0.11
(p-value vs. placebo)		(0.606)	(0.405)	(0.031)*	(0.178)
FVC (L)	0.00	0.09	0.10	0.20	0.08
(p-value vs. placebo)		(0.158)	(0.101)	(0.003)*	(0.193)
$FEF_{25-75\%}$ (L/sec)	0.07	0.10	0.08	0.23	0.20
(p-value vs. placebo)		(0.732)	(0.869)	(0.103)	(0.175)
Proportion of Patients Discontinued (%)	39	21	21	19	31
(p-value vs. placebo)[4]		(0.011)*	(0.008)*	(0.004)*	(0.286)

[1] Data sources: Tables 8.1.4.1, 8.1.4.4.1.1, 8.1.4.4.2.1A, 8.1.4.4.2.3 and 8.1.4.4.2.4.
[2] Mean change adjusted for center effect.
[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.

8.2 Study CR-3069: A Study of Three Dose Levels of Once-A-Day Budesonide (Pulmicort) Nebulizing Suspension and Placebo in Asthmatic Children Aged Eight Years and Younger.

8.2.1 Objectives

[38:51]
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 once a day, versus placebo, in pediatric non-GCS dependent asthmatic patients aged six months to eight years.

8.2.1.1 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.

8.2.1.2 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) 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 PEFs.
- 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.

8.2.1.3 Safety Variables

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

8.2.2 Design

[38:51-3]
This was a multicenter randomized, double-blind, placebo-controlled, parallel-group study. A total of 359 patients were randomized at 26 centers located throughout the USA.

Eligible patients initially entered a two-week baseline phase, which was followed by a 12-

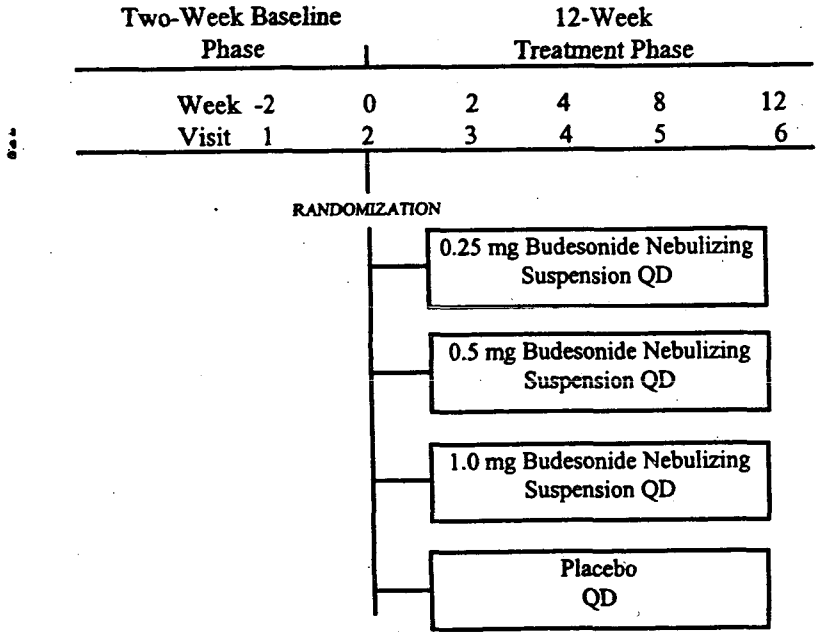
week treatment phase. On entry into the study (Visit 1) patients underwent several screening evaluations and were provided with a diary card to record on a daily basis nighttime and daytime asthma symptom scores, and daily use of bronchodilator therapy. At the end of the baseline phase (Visit 2) eligible patients discontinued taking their chronic asthma medications and were randomized to receive one of the following treatments:

- budesonide nebulizing suspension, 0.25 mg QD
- budesonide nebulizing suspension, 0.50 mg QD
- budesonide nebulizing suspension, 1.0 mg QD
- placebo

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

Patients who successfully completed the 12-week treatment phase were eligible to enter an optional 52-week extension phase to assess the long-term efficacy and safety of budesonide nebulizing suspension. Results of the extension phase of this study will be presented in a separate report (Study 04-3069B).

Figure 8.2.2. Study Design. [38:52]



8.2.3 Protocol

The protocol of this study was very similar to that of Study 04-3100. In this study, only budesonide QD regimens were studied and only non-GCS dependent asthmatic patients were recruited.

8.2.3.1 Selection of Study Population

[38:54-6]
Patients who fulfilled the inclusion and exclusion criteria given below were eligible for enrollment into the study.

8.2.3.1.1 Inclusion Criteria

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

- Daily use of at least one chronic asthma medication (other than corticosteroid) and periodic use of a breakthrough medication (short-acting inhaled bronchodilator) for at least three months prior to Visit 1.
- No long-acting inhaled β_2-agonists within 14 days (instead of 7 days) prior to Visit 1.

8.2.3.1.2 Exclusion Criteria

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

8.2.3.2 Study Drugs

[38:57]
Same as those in Study 04-3100 (Section 8.1.3.2).

8.2.3.3 Prior and Concomitant Treatments

[38:60]
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.
- No inhaled steroids within 30 days prior to Visit 1.

8.2.3.4 Efficacy Measurements and Variables

[38:61-6]
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 8.2.3.4.1-2.

8.2.3.4.1 Procedures at the Clinic

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

- Two measures of child health status (Modified Functional Status II (R) and RAND General Health Index) were completed by the patient's legal guardian (Visits 2, 4 and 6). These assessments were made prior to any other procedures being done at scheduled clinic visits.

8.2.3.4.2 Assessments at Home

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

- 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 week during the treatment phase. Assessments included: days lost from work by the legal guardian; disruption of normal daily routine by the legal guardian; days lost from school/day care by the patient; number of unscheduled visits/phone calls to the physician; number of urgent care/emergency room visits; and number, length and cause of hospitalizations. The diaries were reviewed on Visits 2-6.

8.2.3.5 Safety Measurements and Variables

[38:61-6]

8.2.3.5.1 Procedures at the Clinic

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

8.2.3.6 Adverse Events (AEs)

[38:66-9]
Same as those in Study 04-3100 (Sections 8.1.3.6 - 8.1.3.6.3).

8.2.3.7 Treatment and Measurement Discontinuation

[38:56]
Same as those in Study 04-3100 (Section 8.1.3.7).

8.2.3.8 Statistical Analysis

[38:70-7]

8.2.3.8.1 Analytical Plan

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

8.2.3.8.2 Handling of Dropouts

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

8.2.3.8.3 Statistical Methods

8.2.3.8.3.1 Statistical Methods: Efficacy Variables

8.2.3.8.3.1.1 Primary Efficacy Variables - Nighttime And Daytime Asthma Symptom Scores

[38:72-4]
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

8.2.3.8.3.1.2 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).

8.2.3.8.3.1.3 Secondary Efficacy Variables - FEV_1, FVC, $FEF_{25-75\%}$, Evening and Morning PEFs (in the subpopulation of patients who were able to perform the tests correctly)

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

8.2.3.8.3.1.4 Secondary Efficacy Variables - Child Health Status, Modified FS-II (R)

[38:75, 39:206]

Both the modified Functional Status-II (R) General and Specific scores were calculated. Changes in summary scores from baseline to treatment phase for the budesonide groups compared to placebo were analyzed using ANOVA techniques.

A higher modified FS-II (R) General score indicated a healthier status. A higher modified FS-II (R) Specific score reflected a closer relationship of the functional health status score to the asthma symptoms.

8.2.3.8.3.1.5 Secondary Efficacy Variables - Child Health Status Questionnaire; RAND General Health Index

[38:75-6, 39:207]

Four summary scores were calculated, namely, a RAND-1 score based upon the sum of the values for questions 1-3, a RAND-2 score based upon the sum of the values for questions 4A-4D, a RAND-ALL score based upon the summation of all items of the questionnaire, and a Global RAND Score based upon the score for question 1. A higher score reflected a healthier status.

Changes in summary scores from baseline to treatment phase for the budesonide groups compared to placebo were analyzed using ANOVA techniques.

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

8.2.3.8.3.1.6 Secondary Efficacy Variables - Health Resource Utilization Variables and Indirect Economic Endpoints:

[38:76, 39:287]

Differences in health resource utilization and indirect economic endpoints were analyzed using descriptive statistics, including: hospitalizations; emergency department visits; unscheduled office visits; and indirect costs associated with lost days of school, daycare, caregiver work absence or days of interrupted routine.

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

8.2.3.8.3.2 Statistical Methods: Safety Variables

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

8.2.4 Results

8.2.4.1 Patient Disposition

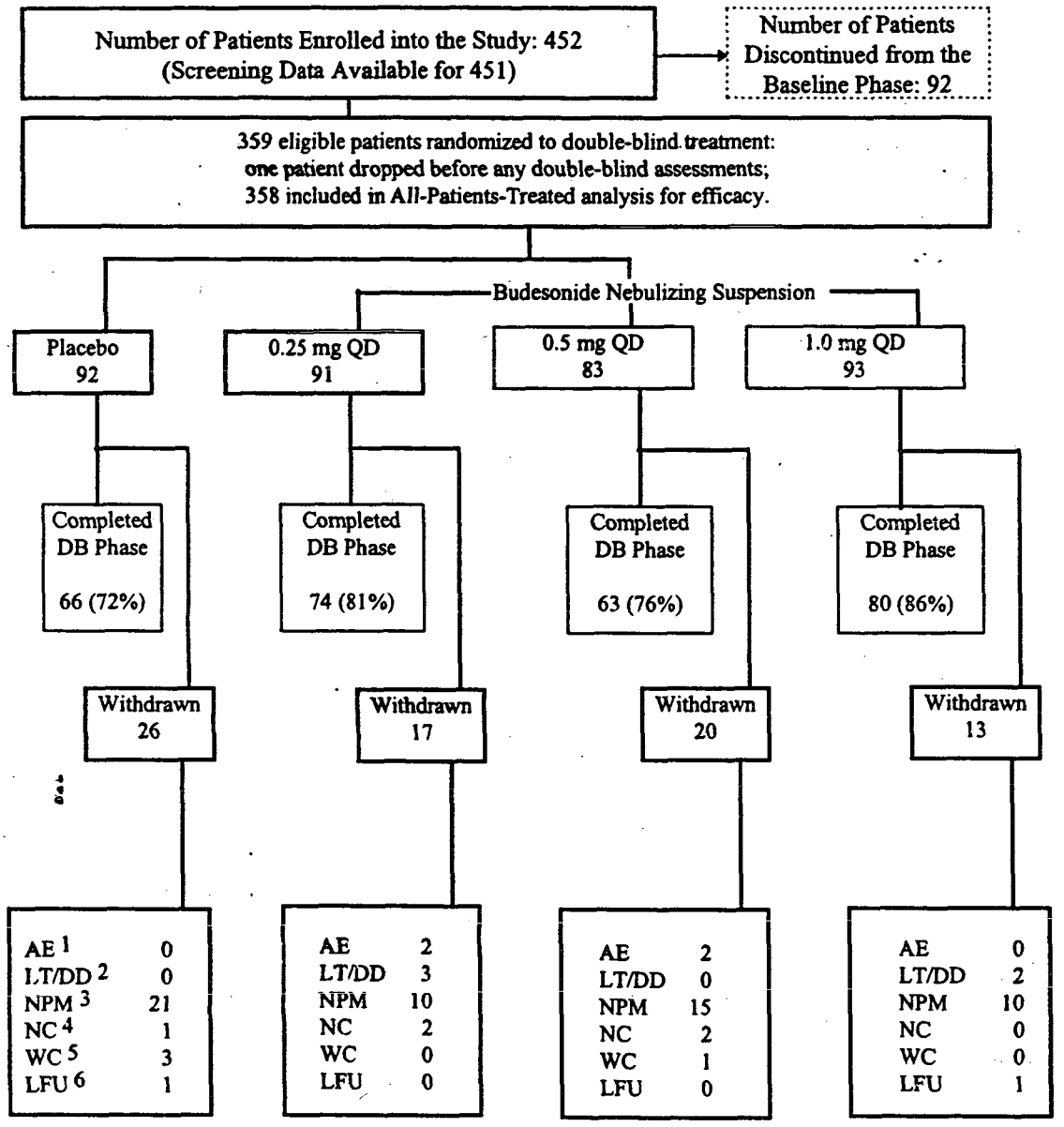
[38:78-82]

The first patient was enrolled into the study in August, 1994. The last patient completed the study in December, 1995. The disposition of patients enrolled into the study is summarized in Figure 8.2.4.1. Of the 451 patients who entered the study, 92 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 (35% of patients). [38:39, 111-4]

A summary of patient disposition for all 359 randomized patients is presented in Table 8.2.4.1. A total of 76 patients were discontinued from the treatment phase of the study. The proportion of patients who were discontinued from the placebo group (28%) was greater than that for the budesonide groups (14-24%). The proportion of patients in the placebo group discontinuing due to worsening asthma (23%) was also greater than that for the budesonide groups (13-17%).

The APT analysis was conducted on 358 patients. One randomized patient was excluded from the APT analysis because this patients was lost to follow-up and no assessments made after the patient had received a single dose of study medication. Of 359 patients randomized, six were judged to be completely non-evaluable for the Per Protocol analysis and 64 were partially evaluable. The most frequent reason for partial non-evaluability was "patient took short-term steroid." [38:122-5]

Figure 8.2.4.1. Disposition of Patients. [38:80]



[1] AE = Adverse Event,
[2] LT = Lack of Therapeutic Effect / DD = Disease Deterioration
[3] NPM = Non-Protocol Use of Medication;
[4] NC = Non Compliance with Study Procedures
[5] WC = Withdrew Consent
[6] LFU = Lost to Follow-up

Table 8.2.4.1 . Summary of patient disposition. [38:81]

Number of Patients	Placebo	Budesonide Nebulizing Suspension QD		
		0.25 mg	0.5 mg	1.0 mg
Randomized	92	91	83	93
Completed Double-Blind Treatment	66 (72%)	74 (81%)	63 (76%)	80 (86%)
Total No. Patients Discontinued:	26 (28%)	17 (19%)	20 (24%)	13 (14%)*
Worsening Asthma[1]	21 (23%)	13 (14%)	14 (17%)	12 (13%)
Adverse Event	0 (0%)	2 (2%)	2 (2%)	0 (0%)
Use of Medication Excluded by Protocol[2]	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Non-Compliance w/Study Procedures	1 (1%)	2 (2%)	2 (2%)	0 (0%)
Withdrew Consent	3 (3%)	0 (0%)	1 (1%)	0 (0%)
Lost to Follow-up	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Evaluated for Efficacy Analyses				
APT/PP[3]	92/90	91/89	82/81	93/93
Evaluated for Safety	92	91	83	93

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

[2] Steroid medications for indications other than worsening of asthma.

[3] Individual patient data were partially excluded from per protocol efficacy calculations for 22, 13, 18 and 11 patients in the placebo, 0.25 mg QD, 0.5 mg QD and 1.0 mg QD groups, respectively.

Data Source: [38:115-8; Section 14.1.1, Tables 3 and 4]

* p=0.020, versus placebo.

8.2.4.2 Demographic and Other Baseline Characteristics

[38:82-3]

The basic demographic characteristics of the study population are summarized in Table 8.2.4.2. The basic demographic characteristics were similar for the four treatment groups.

Reviewer's Comments: 1. Only 6 patients in this study were younger than 11 months old and 14 younger than one year old. These were less than the targeted enrollments (n=18 and 21, respectively). 2. The male to female ratio in this study is typical of asthma patients in this age group.

Table 8.2.4.2. Demographic characteristics. [38:83]

Variable	Placebo	Budesonide Nebulizing Suspension QD			
		0.25 mg	0.5 mg	1.0 mg	Total
n	92	91	83	93	359
Gender:					
Male	60 (65.2%)	63 (69.2%)	58 (69.9%)	56 (60.2%)	237 (66.0%)
Female	32 (34.8%)	28 (30.8%)	25 (30.1%)	37 (39.8%)	122 (34.0%)
Age (months):					
Mean ± SD	59.9±26.6	55.2±25.5	52.4±27.9	56.0±27.2	56.0±26.8
Range	5-103	7-107	10-107	6-107	5-107
Race:					
Caucasian	70 (76.1%)	66 (72.5%)	58 (69.9%)	67 (72.0%)	261 (72.7%)
Black	12 (13.0%)	15 (16.5%)	15 (18.1%)	14 (15.1%)	56 (15.6%)
Hispanic	9 (9.8%)	7 (7.7%)	7 (8.4%)	7 (7.5%)	30 (8.4%)
Oriental	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)	1 (0.3%)
Other	1 (1.1%)	2 (2.2%)	3 (3.6%)	5 (5.4%)	11 (3.1%)
Weight; Mean ± SD					
Pounds	45.0±14.2	43.2±15.9	40.0±14.0	43.3±15.9	42.9±15.1
Kilograms	20.4±6.4	19.6±7.2	18.1±6.3	19.6±7.2	19.5±6.8
Height (cm):					
Mean ± SD	110.4±16.4	106.9±16.4	103.7±18.3	107.9±15.9	107.3±16.8

Source: [38:127-31; Section 14.1.2, Table 1]

8.2.4.2.1 Baseline Asthma Symptom Scores and Pulmonary Function Test Data

[38:83-5,127-31]

The mean duration of asthma at entry into the study, baseline asthma symptom scores, and PFT data (including FEV_1 and PEF) are summarized in Table 8.2.4.2.1.

There were some differences between the treatment groups in nighttime and daytime asthma symptom scores, in FEV_1 and FVC. The highest nighttime and daytime asthma symptom scores were noted in the 0.25 mg QD budesonide group, the lowest FEV_1 in the 1.0 mg QD budesonide group, and the highest FVC in the placebo group.

Table 8.2.4.2.1. Baseline lung function and asthma symptom scores. [38:84]

Variable	Placebo	Budesonide Nebulizing Suspension QD			
		0.25 mg	0.5 mg	1.0 mg	Total
n	92	91	83	93	359
Duration of Asthma (months)					
Mean±SD	37.1±22.0	35.4±22.4	36.7±25.1	36.1±24.4	36.3±23.4
Range	5-92	5-97	5-107	5-107	5-107
Nighttime Asthma Symptom Scores:					
Mean±SD	1.08±0.63	1.32±0.65	1.19±0.64	1.19±0.58	1.19±0.63
Daytime Asthma Symptom Scores:					
Mean±SD	1.27±0.52	1.44±0.56	1.33±0.52	1.31±0.52	1.34±0.53
Spirometry Able:					
No	54 (58.7%)	62 (68.1%)	54 (65.1%)	60 (64.5%)	230 (64.1%)
Yes	38 (41.3%)	29 (31.9%)	29 (34.9%)	33 (35.5%)	129 (35.9%)
PEF Able:					
No	36 (39.1%)	47 (51.6%)	41 (49.4%)	38 (40.9%)	162 (45.1%)
Yes	56 (60.9%)	44 (48.4%)	42 (50.6%)	55 (59.1%)	197 (54.9%)
FEV_1:	1.27±0.31	1.23 ±0.29	1.22 ±0.31	1.13 ±0.26	1.21 ±0.30
(n)	(38)	(29)	(29)	(33)	(129)
% Predicted	81.6 ±17.3	83.8 ±20.3	81.9±14.8	78.3 ±15.5	81.3±17.0
(n)	(39)	(29)	(29)	(33)	(130)
% Reversibility	27.0±11.5	26.1±15.2	31.6±15.7	26.3±13.2	27.7±13.8
FVC:	1.61±0.33	1.53±0.38	1.47±0.43	1.42±0.34	1.51±0.37
(n)	(38)	(29)	(29)	(33)	(129)
Morning PEF (L/min):					
(n)	(55)	(44)	(41)	(55)	195)
Mean±SD	143.9±45.4	142.4±45.5	137.5±45.6	130.8±38.3	138.6±43.6
Evening PEF (L/min):					
(n)	(55)	(42)	(41)	(54)	(192)
Mean±SD	150.7±45.2	151.5±45.6	149.2±49.2	136.9±39.2	146.7±44.7

Data Source: [38:127-31; Section 14.1.2, Table 1]

8.2.4.2.2 Baseline Physical Examination, Previous and Concomitant Diseases

[38:85, 132-7]

The majority of patients were normal for most physical examination assessments. Approximately half of the patients had abnormalities in the nasal/other parameter. The