Reviewer Comment
The open-label nature of this study may have led patients on one arm to be more likely to drop out than patients on the other arm. In fact, 9 patients dropped out the day they were randomized. Five of these patients had previously been on BNS and were randomized to Conventional (see Figure 6 above). The fact that patients and the investigators decided whether the patient continued decreases the validity of the results of the study. Essentially, the patients in the study were self-selected. The study report did not state whether subjects knew their double-blind treatment assignment prior to enrolling in the open-label phase, nor how many patients were eligible to continue but chose not to. An amendment to the protocol appears to indicate that the patients were not unblinded to their Study 3069 treatment before entering the open-label phase. [4]

2.2.1.2 Entrance Requirements

If the patients met the entrance requirements for the open-label phase, participation was optional. The entrance requirements were:

1) Completing the double-blind phase;
2) The patient's health would not be compromised by participating in the open-label phase, per the judgment of investigator;
3) The patient and/or legal guardian was able to comply with the protocol procedures; and
4) The legal guardian read, understood and signed the consent form for the open-label phase.

A subsequent amendment (dated March 14, 1995) allowed patients who dropped out of the double-blind phase due to lack of effect to enter the open-label phase. This amendment was not retroactive, i.e., the study participants who had dropped out of the double-blind phase prior to the amendment were not asked to return and enter the open-label phase. The study report did not state how many patients this affected.

Reviewer Comment
The patient population was enriched due to the fact that some Study 3069 dropouts were not allowed to enter the study. The amendment that allowed dropouts to enter, after some patients had already dropped out, changed the composition of the patient population. It is unknown what percentage of patients who had previously dropped out of Study 3069 were in each treatment group in Study 3069b. One treatment group may have had a different composition of Study 3069-completer patients and Study 3069-dropout patients than the other. This is a factor that may have confounded the results.

2.2.1.3 Time of Day of Measurement

The infants were measured with a recumbant table and the standing children with a wall mounted stadiometer. According to the original protocol, all patients were to report to the clinic between 6 am and 9 am. (Patients whose cortisol levels were being assessed were supposed to report by 8 am.) An amendment to the protocol (dated March 14, 1995 added 5 months after the first patient had enrolled) allowed patients whose cortisol levels were not being measured and who could not perform PFTs to report to the clinic *at any time of day.*

[4] An amendment to the protocol (dated June 29, 1994) stated that the randomization of patients to the open-label treatments would "no longer be" stratified by the patients double-blind treatment. "This ...avoids any potential bias in unmasking the double-blind treatments." The study enrolled the first patient in October 1994. Therefore, it appears that the patients did not know their double-blind treatment when they enrolled into the open-label phase.

Reviewer Comment
The literature suggests that height, within patient, varies as much as 0.6 cm over the course of one day (Werther, The Lancet, Volume 351, 1998) for standing children. There were 169 patients who were too young to perform PFTs but were old enough to be measured standing (≥ 1 year). A variable for the time of day of the measurements was not included in the electronic datasets the sponsor submitted. Therefore, time of day cannot be accounted for in the analysis. Analyses of change from baseline using only two measurements may be sensitive to differences of 0.6 cm. However, analyses that use all the patients' data (up to 8 measurements) should be more robust to such small differences.

2.2.1.4 Prednisone Use

Although no inhaled glucocorticosteroids (other than study drug) were allowed in the open-label phase, intermittent courses of oral prednisone were allowed for the control of asthma exacerbations, as judged by the investigator. Oral prednisone at relatively modest doses (3-5 mg/m^2/day) has been previously reported to impair growth in children, (Allen, *The Endocrinologist*, 1998). The treatment group with the higher rate of use may have been affected to a greater extent. The prednisone use results are examined on page 30.

2.2.2 Results

2.2.2.1 Demographics & Baseline Height

The treatment groups were similar with respect to gender, age and baseline height.

Table 9: Demographics

	Conventional (n=90)	**BNS (n=182)**
Gender		
Male	57 (63%)	125 (69%)
Female	33 (37%)	57 (31%)
Age (months)		
mean ± std dev.	60.4 ± 26.3	58.4 ± 26.2
range	11-111	8-111
Height (cm)	n=89 *	n=179*
mean ± std dev.	108.1 ± 17.6	106.4 ± 16.5

*Four patients did not have baseline height measurements.

2.2.2.2 Sponsor's Presentation of the Data

2.2.2.2.1 Analyses

The sponsor did not pre-specify specific analyses in the study protocol for the height measurements.

The sponsor stated in the study report that descriptive statistics of the results of the study would be presented using three different endpoints. The three endpoints were:

1) number of centimeters difference between observed height of each visit and the standard median height (based on gender and exact chronological age) at baseline and each subsequent visit;
2) percent of patients below standard median height at baseline and each subsequent visit;
3) slopes of height over time estimated using a separate regression equation for each patient with height as the dependent variable and time (month) as the independent variable.

After this reviewer was unable to replicate the analyses, the sponsor clarified the first and third endpoints in more detail in teleconferences on 3/25/98 and 3/27/98, and a fax on 3/27/98. Below is a summary of the sponsor's explanation of the first and third endpoints.

Endpoint #1: The following ratio, called a **"z-score"** was calculated for each patient at baseline and each subsequent visit:

$$\frac{\text{(Observed Height) - (NCHS Standard Median Height for age at baseline)}}{\text{standard deviation}}$$

where NCHS stands for National Center for Health Statistics, and the standard deviation equals:

$$\frac{\text{(NCHS Standard 95 percentile height - 5 percentile height)}}{2 \times 1.645}$$

(The sponsor referenced the [redacted] Software Package from [redacted] for the formula of this standard deviation.[5]) The endpoint was the difference between the two ratios. The sponsor then accounted for time on study; the ratio was standardized by the number of days the patient was on study drug. The difference between the baseline ratio and the final visit ratio was termed the "change from baseline" analysis or the "z-score analysis". This change was the dependent variable in an ANOVA with center and treatment as factors and baseline z-score as a covariate.

Endpoint #3: The patients' **slopes** of height over time were estimated using a separate regression equation for each patient with the z-scores for each patient (calculated the same as described above) as the dependent variable and time (month) as the independent variable. The slopes were then analyzed using an ANOVA with center and treatment as factors and baseline z-score as a covariate.

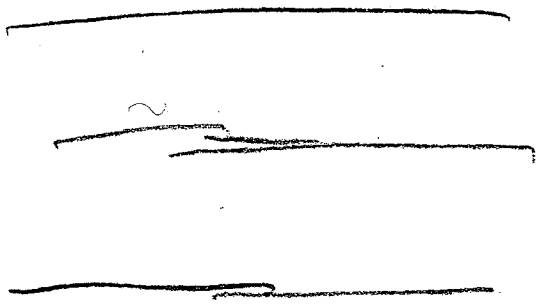
[redacted]

[5] The software package and formula have not been validated by this reviewer.

2.2.2.2.2 Dataset

The sponsor stated that only the data from patients who completed 52 ± 4 weeks of the study would be used in the calculations (n=213). Therefore, the sponsor excluded patients who did not complete at least 336 days on study drug (n=59)[6]. The sponsor also excluded patients who did not have a baseline height measurement (n=3). In addition, the sponsor excluded Patient #02-0234. The last two measurements of this four-year old female BNS patient, #02-0234, were unlikely given her age and her previous measurements, see figure below. Her estimated growth rate was 38.3 cm/year. The sponsor contacted the site and the site verified the information as correct. The sponsor excluded all the height measurements for this patient as the data were thought to be unreliable. Therefore, the sponsor's dataset was further reduced by 1 patient, yielding a total of 209 patients.

Patient #02-0234



2.2.2.2.3 Results

The sponsor stated that no difference in growth rate was observed between the treatment groups. The following results were stated in the study report.

[6] Two BNS patients completed 371 days and 361 days of visits, but stopped taking the study drug before day 336. Therefore, these two patients were excluded.

First Endpoint

The sponsor presented the following table:

Table 10: The Sponsor's Table, excerpted from the study report appendix section 14.3.5 Table 14

	n	Mean Baseline (cm/yr)	Mean Change (**) ± Std Dev (cm/yr)	Difference	p-value *
BNS	151[a]	107.65	6.55 ± 2.08		
Conventional	58	108.10	7.39 ± 2.51	0.84	0.233 [b]

Sponsor's Footnotes to the table: * P-value based on an analysis on standardized height.
** Mean changes adjusted for center effect.

Reference: Excerpted from Sponsor's Table in Appendix to the Study Report, Section 14.3.5 Table 14

Reviewer's Footnotes to the table:

[a] The sponsor reported n=151 in the appendix and n=150 in the study report and the draft report that was sent to the advisory committee. In a teleconference on 3/25/98 the sponsor confirmed that this was a mistake and that the actual number was n=151.

[b] This p-value is not associated with the means in this table. The sponsor confirmed that the p-value belonged to a different analysis. Further, the sponsor stated that a mistake in the calculations had been made and the p-value was actually less than 0.05 (p=0.0031)..

In a teleconference on 3/25/98, the sponsor stated that the means in the table were least square means from an ANOVA on change from baseline of the height measurements (not the z-scores) adjusted for center and baseline height. The p-value was from an analysis of variance on the change in the z-scores adjusted for center and baseline z-score. In a teleconference on 3/27/98, the sponsor stated that a mistake in the calculation of the standard deviation of the z-scores had been found. With the revised standard deviation, the p-value was less than 0.05 (p=0.0031).

Second Endpoint

The results of the number and percent of patients above and below the standard median height at baseline as compared to the final visit are summarized in Table 11 below. Higher percentages in Columns 2 and 4 indicate higher percentages of patients reaching heights greater than the standard tables predict.

Table 11: Percentages of Patients that started out below the Standard Median Height For Their Age and Switched to Above & Percentages of Patients that started out above the Standard Median Height For Their Age and Stayed Above

	Column 1	Column 2	Column 3	Column 4
	Total n started out below	# (%) that switched to above	Total n started out above	# (%) that stayed above
BNS	70	4 (5.7%)	83	72 (86.7%)
Conventional	25	2 (8.0%)	33	28 (84.8%)

Third Endpoint

The sponsor presented the results of the third analysis (slopes of z-scores over time) in the fax on 3/27/98. The p-value for the treatment effect was statistically significant in models with treatment,

center, and baseline z-score (p=0.002). A similar treatment effect and significance level were found in a model without baseline z-score.

2.2.2.3 Reviewer's Comments

The company presented results of completers analyses that used growth velocity slopes standardized for the standard median height of each patient. This reviewer performed additional analyses on the data to determine the sensitivity of the results to the statistical methodology selected and the patients selected. In summary, it appears that the results are not sensitive to the type of analysis, but are sensitive to the patients selected (completers vs. all patients treated).

2.2.2.3.1 Analyses

The analyses performed for this review are analyses of slopes of height over time estimated using a separate regression equation for each patient with height as the dependent variable and time as the independent variable. The mean slopes are then compared across treatment groups. A similar analysis, a repeated measures analysis of variance, is also presented in this review. Models including age and gender were performed to adjust for differences in age and gender across treatment groups. (The sponsor similarly adjusted for these factors using the NCHS median heights for each patient based on his/her age and gender.) In summary, the results presented below will show that age is highly predictive of height, but cannot explain all of the variability in height. It appears that the growth rates are different between the two treatment groups even after accounting for age and gender.

A slope analysis is more appropriate for this data than analysis based on change from baseline because the latter uses only two measurements (baseline and last visit). The data within patient were highly variable for several patients, (see individual patient graphs in the appendix, pp. 61-68). Several patients had baseline and final visit measurements that appeared to be about five to ten centimeters too high or too low based on the other measurements for these patients (ie: Patients #05-0250 and 18-0331). Analyses of change from baseline using only two measurements may be more sensitive to measurement error than an analysis on slopes that uses all available data. This should be considered when reviewing the evidence of the treatment effect from the sponsor's change from baseline analyses.

2.2.2.3.2 Datasets

The company's analyses excluded patients who dropped out before 48 weeks (n= 59). There was a large (20%) differential dropout rate (BNS: 14%; Conventional: 32%). Further, the percentage of dropouts due to lack of effect was different for the two treatments (Conventional: 14%; BNS: <1%). One of the sponsor's methods of analysis, an analysis on individual slopes, lends itself to including subjects with less than complete data. For the most part, both dropouts and completers appear to have grown linearly over time, (see individual patient data graphs in appendix). This argues for inclusion of subjects with at least 3 datapoints into an analysis of slopes, (adding 33 patients to the dataset). This reviewer performed both Completers and All Patients Treated analyses on the data. The following two sections describe the different datasets.

Completers

For the reviewer's completers analysis, four patients were added to the sponsor's cohort of 209 patients. The sponsor excluded 3 patients with no baseline data. This reviewer estimated the slopes of these patients using the visits subsequent to baseline. The sponsor also excluded all data from Patient #02-0234 because it was believed to be unreliable. This reviewer excluded the last two observations from Patient #02-0234 that appeared to be the only unreliable portion of the data and kept the remaining measurements. Therefore, the number of patients in the reviewer's completers analyses is 4 patients greater than that of the sponsor's completers analyses (n=213).

All Patients Treated

For the reviewer's "All Patients Treated" (APT) analyses, this reviewer included patients with at least 3 measurements. This added 33 more patients to the dataset. Two of these patients with only 3 measurements had unreliable data. The last measurement of Patient #03-0389 was [redacted] greater than the previous measurement (56 days prior). This patient was an 18 month old male on BNS with an estimated growth velocity of 28.3 cm/year. The last measurement of Patient #27-0543 was less than that of the previous two measurements. This patient was a 63 month old male on Conventional treatment with an estimated growth velocity of -1.65 cm/year. Both of these estimates are unlikely and both were the two extreme values in the dataset (see bar charts in appendix, pages 58-59). Excluding both patients from the dataset increases the estimated treatment effect, therefore, analyses with and without these patients are presented in this review.

2.2.2.3.3 Reviewer's Results

The mean slopes for the different treatment groups for both completers (patients who completed at least 48 weeks) and dropouts (patients who withdrew before week 48) are graphed in the appendix, page 60. In general, the dropouts grew at a faster rate than the completers.[7] The BNS dropouts grew at a slightly faster rate than the Conventional treatment dropouts.

The results of the analyses appear to demonstrate a 0.76 - 0.85 cm/year difference in growth velocity, depending on the patients included, see Table 12.

APPEARS THIS WAY
ON ORIGINAL

[7] The slopes for the patients who completed the study were calculated using all the weeks; one could argue that the rate of growth of the completers until week 48 was similar to that of the dropouts until week 48. However, the mean of the slopes calculated using only the weeks before 48 was similar to that calculated using all the weeks (6.64 cm/yr using weeks 1-47; 6.63 cm/yr using all the weeks).

Table 12: Analyses of Estimates of Individual Patient Slopes of Height Over Time

	N	Mean ± SD	Estimate	95% CI	p-value
Sponsor's Completers [a]					
-BNS	151	6.50 ± 1.9			
-Conventional	58	7.33 ± 2.4	.83	(.21, 1.45)	0.0094
Total:	209				
Reviewer's Completers [b]					
-BNS	155[a]	6.48 ± 1.9			
-Conventional	58	7.33 ± 2.4	.85	(.23, 1.46)	0.0073
Total:	213				
All Patients Treated #1 [c]					
-BNS	172	6.75 ± 2.9			
-Conventional	74	7.27 ± 2.9	.51	(-.28, 1.31)	0.2033
Total:	246				
All Patients Treated #2 [d]					
-BNS	171	6.63 ± 2.4			
-Conventional	73	7.39 ± 2.7	.76	(.075, 1.45)	0.0299
Total:	244				

[a] Sponsor's Completers includes all patients who completed at least 48 weeks of the study and had a baseline value, except patient #02-0234 who had unreliable data.

[b] Reviewer's Completers includes all the patients who had completed at least 48 weeks of the study. The slopes of patients without a baseline measurement were estimated using the remaining measurements. The slope of patient #02-0234 was estimated using a portion of the data which appeared to be reliable.

[c] All Patients Treated #1 includes all patients who had greater than 2 measurements.

[d] All Patients Treated #2 includes all patients who had greater than 2 measurements except patients #03-0389 and #27-0543, see discussion in text.

Age is a strong predictor of growth, therefore age was included in the model. Gender was included as well to examine possible differences between genders, see Table 13 below. The age effect was negative and highly statistically significant indicating that the younger patients tended to grow faster. The estimate of the gender effect was negative meaning the models estimated that the girls grew at a rate 0.4-0.5 cm faster than the boys. While these were strong prognostic factors, the treatment effects and associated p-values from these models were similar to those in the models without age and gender.[8]

[8] The R^2 was ≈.02 in the models without age and ≈.30 in the models with age.

Table 13: Analyses of Estimates of Individual Patient Slopes of Height Over Time Including Age and Gender in Models

	Factor	Estimate	95% CI	p-value
Sponsor's Completers [a]				
Model 1: Trt & Age	Drug	.86	(.35, 1.38)	0.0011
	Age	-.046	(-0.055, -0.037)	0.0001
Model 2: Trt, Age, & Gender	Drug	.83	(.32, 1.34)	0.0016
	Age	-.046	(-.055, -.037)	0.0001
	Gender	-.49	(-.98, -.0074)	0.0466
Reviewer's Completers [b]				
Model 1: Trt & Age	Drug	.86	(.35, 1.37)	0.0010
	Age	-.045	(-.054, -.036)	0.0001
Model 2: Trt, Age, & Gender	Drug	.84	(.33, 1.34)	0.0013
	Age	-0.46	(-.054, -.037)	0.0001
	Gender	-.47	(-.95, .0023)	0.0511
All Patients Treated #1 [c]				
Model 1: Trt & Age	Drug	.60	(-.081, 1.29)	0.0837
	Age	-.057	(-.070, -.045)	0.0001
Model 2: Trt, Age, & Gender	Drug	.60	(-.085, 1.28)	0.0858
	Age	-.058	(-.070, -.046)	0.0001
	Gender	-.62	(-1.29, .043)	0.0667
All Patients Treated #2 [d]				
Model 1: Trt & Age	Drug	.83	(.25, 1.41)	0.0052
	Age	-.052	(-.063, -.042)	0.0001
Model 2: Trt, Age, & Gender	Drug	.82	(.25, 1.39)	0.0053
	Age	-.053	(-.063, -.042)	0.0001
	Gender	-.68	(-1.24, -.12)	0.0178

[a] Sponsor's Completers includes all patients who completed at least 48 weeks of the study and had a baseline value, except patient #02-0234 who had unreliable data.

[b] Reviewer's Completers includes all the patients who had completed at least 48 weeks of the study. The slopes of patients without a baseline measurement were estimated using the remaining measurements. The slope of patient #02-0234 was estimated using the reliable portion of the data, see discussion in text.

[c] All Patients Treated #1 includes all patients who had greater than 2 measurements.

[d] All Patients Treated #2 includes all patients who had greater than 2 measurements, except patients #03-0389 and #27-0543, see discussion in text.

Interaction Effects

Models including an age-by-treatment and a gender-by-treatment interaction were performed as well. The estimates of the age-by-treatment interaction effect were small (≈ -.02), but hinted at a possible differential treatment effect (p=.1153). The negative estimate means that the drug may have a more pronounced effect on younger children. An analysis that included only children less than 2 years old and who completed at least 48 weeks of the study (BNS n=11; Conventional n=8) was performed to further investigate this possible interaction. This analysis found a larger treatment effect (2.75 cm/year) that was statistically significant (p=0.0161). However, this effect appeared to be sensitive to

differences in the patients selected.[9] Additional analyses were performed on the children ages 2-4 and 5-8. The treatment effects were similar for the two older age groups (approximately 0.5 cm/year).

Additional Factor: Prednisone

Prednisone was used in the study on an as-needed basis. Since prednisone has been reported to affect growth velocity, the treatment group with the higher rate of use may have been affected to a greater extent. A higher percentage of patients on the Conventional treatment arm used prednisone at least once, see Table 14 below. However, the patients who used prednisone an average of 2.5 mg or more per day were all on BNS (n=9). Therefore, it is difficult to hypothesize the direction of the bias prednisone may have introduced. The use of prednisone in the trial may have over- or under-estimated the treatment effect.

Table 14: Percent of Patients Who Use Prednisone At Least Once During Study

	BNS	Conventional
Sponsor's Completers Dataset[1]	76/150 (51%)	35/58 (60%)
Reviewer's Completers Dataset[2]	78/153 (51%)	35/58 (60%)
Reviewer's APT Dataset #1	84/170 (49%)	45/74 (61%)
Reviewer's APT Dataset #2	84/169 (50%)	45/73 (62%)

1 One BNS patient in the sponsor's completers dataset had missing values for the prednisone data.

2 Two BNS patients in the reviewer's completers dataset and the reviewer's APT datasets had missing values for the prednisone data.

The factors "total number of days used prednisone" and "average daily use of prednisone" were included in the model, and not found to be statistically significant. The estimate of the treatment effect did not change.

The literature suggests that the effect of corticosteroids on growth velocity in children may be more pronounced in the younger patients. It is unknown if the putative growth impairment effect of prednisone is different for different age groups. Since age increased with time on study, adjusting for the effect of prednisone is difficult. Consider two patients who started the study when they were 6 months old. Suppose the first patient used prednisone during the first few months of the study and the second patient used it during the last few months. The prednisone may, in theory, affect the height of the first patient more severely than that of the second patient. The imbalances of percentage of patients using prednisone, together with the unknown, but potentially different effects of prednisone on different ages, creates results which are confounded by an uncontrollable factor.

Repeated Measures ANOVA

A repeated measures ANOVA was performed on the data to determine the sensitivity of the results to the statistical methodology selected.[10] The analyses found similar treatment effects, (estimated effects ranged from 0.76 to 0.83).[11] Unlike the estimated treatment effects from the linear regression on the

[9] The treatment effect was smaller using the "All Patients Treated #2" dataset (1.94, p=0.1489). The treatment effect was even smaller using the "All Patients Treated #1" dataset (0.69, p=0.7487). (The sponsor's completers dataset of children <24 months had the same patients as the reviewer's completers dataset of children <24 months.)

[10] The model was performed in SAS version 6.12, using the PROC MIXED function. In the model, each patient was allowed to have their own intercept and slope. The model assumed a uniform correlation structure. This means that the model assumed the errors were independent over time.

[11] Sponsor's Completers: 0.83 cm/year, p=0.0084; Reviewer's Completers: 0.85 cm/year, p=0.0067; All Patients Treated #1: 0.76 cm/year, p=0.0124; All Patients Treated #2: 0.80 cm/year, p=0.0083).

slopes, the estimated treatment effects from the repeated measures ANOVA on the observed height measurements were statistically significant *no matter which dataset was used* (i.e., the APT analysis including the two patients with aberrant measurements found a statistically significant treatment effect, p=.0124).

2.2.3 Conclusions

On the basis of these results, it appears that in the one year extension of Study 3069 BNS did cause a decrease in growth velocity, especially among children less than 24 months old. However, these findings should be regarded cautiously in the context of the problems with the study design and conduct which may have over- or under-estimated the treatment effect.

3. Label

The following comments refer to the annotated package insert and may be conveyed to the sponsor:

[redacted]

Page 5, Lines 18-27
This study was not submitted in this NDA and not reviewed by this statistician.

Page 9, Lines 22-27 & Page 8, Lines 19-32
The sponsor proposed to claim that [redacted] This was based on the difference between the average of the baseline period and the average of the eighth week. The sponsor did not submit electronic data for this study, therefore, this reviewer entered the line listing data of each patient's average prednisolone dose of the baseline period and the average of Weeks 5-8. (The average of week 8 was not listed in the NDA).

Although this study was not fully reviewed, it is important to evaluate the proposed labeling in the context of the following comments.

- A reviewer's ITT analysis of the mean prednisolone dose reduction between baseline and the average of Weeks 5-8 indicated that there was no statistically significant difference between the two treatments (Placebo: 0.69 mg/kg; BNS: 0.44 mg/kg; p=0.34). The 95% confidence interval for the difference between the two treatment groups was (-0.27, 0.77).[12]

- The study results should be examined cautiously due to the fact that the treatment effects were different across centers:

[redacted]

[12] Six patients had missing values for the average of the second month's prednisolone dose. The value for the average of the first month was used for these patients. In an analysis where these patients were deleted, rather than using imputed values, the difference between the treatment groups was even smaller (95%CI: -0.64, 0.39, p=0.63).

- Center #1: -0.24 mg/kg (placebo superior);
- Center #2: 0.15 mg/kg;
- Center #3: 0.95 mg/kg;

yielding a statistically significant treatment-by-center interaction (p=0.057). It appears as though most of the treatment effect was in Center #3. The significant treatment-by-center interaction potentially compromised the inferences based on study results.

- A reviewer's ITT analysis of the proportions of patients who completely eliminated their use of prednisolone during weeks 5-8 found no statistically significant difference between the two treatment groups, (Placebo: 6%; BNS: 28%, Fisher's Exact Test p-value = 0.1774).

- The protocol did not specify the type of analysis to be used (t-test of means, ANOVA on means with center in the model, test of proportions etc.); nor the endpoint (mean reduction of dose, percentage reduction of dose, percentage who eliminated prednisolone entirely, etc.); nor the timepoint (end of eighth week, average of eighth week, average of seventh and eighth weeks, etc.). In view of the *post-hoc* nature of the analysis, the fact that the results were not robust to changes in method of analysis further detracts from the strength of the results of this study.

From a limited review of the study results, it appears that the study's results do not strongly support the claim that

Asthma control refers to more measures than nighttime and daytime symptoms, some of which were not significantly improved in the BNS group compared to placebo patients. The statement that ' should be changed to more accurately reflect the data.

Graphs

The averages of weeks 0-12 do not add information to the figures.

APPEARS THIS WAY
ON ORIGINAL

/S/

Barbara Elashoff
Mathematical Statistician

concur: Steve Wilson /S/ 5/6/98
Ed Nevius /S/ 5-6-98

cc:
Orig. NDA 20-929
HFD-570 / Division File
HFD-570 / JJenkins, RMeyer, SChu, GTrout
HFD-715 / Chron, division file
HFD-715/ BElashoff, SWilson

4. Appendix

4.1 Baseline Tables

Appendix Table 1: Study 3069 Baseline Scores

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)	(28)	(33)	(128)
% 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
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: Section 14.1.2, Table 1.

Appendix Table 2: Study 3072 Baseline Scores

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±18.3 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: Section 14.1.2, Table 1.

Appendix Table 3: Study 3100 Baseline Scores

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, Volume 19.1, p.45 of 72.

4.2 Demographic Tables

Appendix Table 4: Study 3069 Demographics

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: Section 14.1.2, Table 1.

Appendix Table 5: Study 3072 Demographics

Variable	Placebo	Budesonide Nebulizing Suspension BID			
		.25 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

Source: Section 14.1.2, Table 1.

Appendix Table 6: Study 3100 Demographics

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.

[2] Source: Section 14.1.2, Table 6. WHO highest level name; numbers are not mutually exclusive.

4.3 Secondary Efficacy Variables

Appendix Table 7

Mean Changes from Baseline (Adjusted for Center Effect) Use of Breakthrough Medication

	Placebo	.25 mg QD	.25 mg BID	.5 mg QD	.5 mg BID	1.0 mg QD	1.0 mg BID
3069							
n	92	91		82		93	
mean Δ	-4.19	-6.26		-6.31		-5.98	
p-value		0.017		0.018		0.038	
3072							
n	44		47		42		45
mean Δ	-3.14		-5.56		-6.66		-6.00
p-value			0.032		0.002		0.012
3100							
n	92	93	97		96	93	
mean Δ	-2.36	-4.39	-5.22		-4.92	-4.38	
p-value		0.018	0.001		0.002	0.014	

Studies 3069, 3072 & 3100: The mean reduction in number of days of breakthrough medication use were statistically significantly different between all BNS groups and placebo (at a level of 0.05).

Appendix Table 8: Mean Changes from Baseline (not adjusted for Center Effect) in Number of Puffs of Breakthrough Medication Per Day

		Placebo	.25 mg QD	.25 mg BID	.5 mg QD	.5 mg BID	1.0 mg QD	1.0 mg BID
3069	total n	92	91		82		93	
Nebulizer	n	51	60		57		57	
	mean Δ	**-0.45**	**-0.92**		**-0.69**		**-1.05**	
pMDI	n	26	16		14		25	
	mean Δ	**-0.32**	**-0.66**		**-1.79**		**-1.22**	
3072	total n	44		47		42		45
Nebulizer	n	14		21		15		13
	mean Δ	**-0.04**		**-0.96**		**-1.33**		**-0.72**
pMDI	n	29		26		26		32
	mean Δ	**-0.15**		**-1.10**		**-1.72**		**-1.51**
3100	total n	92	93	97		96	93	
Nebulizer	n	57	55	63		70	64	
	mean Δ	**-0.03**	**-0.40**	-0.69		**-0.87**	**-0.60**	
pMDI	n	21	22	24		18	20	
	mean Δ	**-0.36**	**-1.65**	-1.63		**-0.94**	**-0.71**	

Studies 3069, 3072 & 3100: The mean reduction in number of puffs per day of breakthrough medication was different for different devices. (The patients who used the pMDI device used more puffs per day.) The mean reduction sin number of puffs per day of all the BNS groups were numerically superior to placebo, for both devices.

Appendix Table 9: Mean Changes (Adjusted for Center Effect) in Morning & Evening PEF

		Placebo	.25 mg QD	.25 mg BID	.5 mg QD	.5 mg BID	1.0 mg QD	1.0 mg BID
3069	total n	92	91		83		93	
Morning	# (%) able to use peak flow meter	55 (59.8)	44 (48.3)		41 (49.4)		55 (59.1)	
	mean Δ (L/min)	7.1	14.4		6.5		10.9	
	p-value		0.135		0.901		0.417	
Evening	# (%) able to use peak flow meter	55 (59.8)	42 (46.2)		41 (49.4)		54 (58.1)	
	mean Δ (L/min)	3.6	11.2		3.8		9.9	
	p-value		0.114		0.977		0.169	
3072	total n	44		47		42		45
Morning	# (%) able to use peak flow meter	44		47		42		45
	mean Δ (L/min)	-1.3		15.9		11.8		10.4
	p-value			0.002		0.016		0.030
Evening	# (%) able to use peak flow meter	44		47		42		45
	mean Δ (L/min)	3.0		14.9		11.6		13.2
	p-value			0.042		0.152		0.083
3100	total n	92	93	97		96	93	
Morning	# (%) able to use peak flow meter	32 (34.8%)	32 (34.4%)	34 (35.1%)		29 (30.2%)	34 (36.6%)	
	mean Δ (L/min)	-0.2	10.9	23.0		24.8	17.1	
	p-value		0.165	0.003		0.004	0.030	
Evening	# (%) able to use peak flow meter	32 (34.8)	32 (34.4)	33 (35.1)		29 (30.2)	34 (36.6)	
	mean Δ (L/min)	1.9	16.8	19.2		21.0	14.1	
	p-value		.034	.012		.010	.078	

Study 3069: A total of 195 (54.3%) patients were able to use the peak flow meter. The percentages of patients able to use the meter were similar across treatment groups. The mean changes in **Morning PEF** in the .25 mg QD and the 1.0 mg QD dose groups were numerically superior to placebo. Performed as well as (actually, slightly better than) the 0.5 mg QD dose group. None of the differences were statistically significantly different. The results for the **Evening PEF** were similar to those of the Morning PEF. Again, the placebo group performed as well as the 0.5 mg QD dose group. The mean changes in the 0.25 mg QD and 1.0 mg QD dose groups were numerically superior to that of the placebo group. None of the differences were statistically significantly different.

Study 3072: All patients were able to use the peak flow meter, (patients were between 4 and 8 years old in this study). The mean changes in **Morning PEF** in all BNS groups were numerically and statistically significantly superior to placebo. The results for the **Evening PEF** were similar to those of the Morning PEF. The BNS mean changes were numerically superior to placebo, with a statistically significant difference between the .25 mg BID dose group and placebo (at the .05 level).

Study 3100: Data from patients who were identified on the case report forms as being unable to use the peak flow meter correctly were not used in the analysis. The investigators were trying to train the patients to use the peak flow meters and the data were unreliable. A total of 161 (34.2%) patients were able to use the peak flow meter. The percentages of patients able to use the meter were similar across treatment groups. The mean changes in **Morning PEF** in all BNS groups were numerically superior to

placebo. The .25 mg BID, .5 mg BID and 1.0 mg QD treatment group mean changes were statistically significantly different than placebo (at the .05 level). The results for the **Evening PEF** were similar to those of the Morning PEF. The BNS mean changes were numerically superior to placebo, with the .25 mg QD, .25 mg BID and .5 mg BID dose group differences statistically significant (at the .05 level).

Appendix Table 10: Mean Changes (Adjusted for Center Effect) in FEV_1

	Placebo	0.25 mg QD	0.25 mg BID	0.5 mg QD	0.5 mg BID	1.0 mg QD	1.0 mg BID
3069 total n	92	91		83		93	
# (%) able to perform spirometry	38 (41.3)	29 (31.9)		28 (33.7)		33 (35.5)	
mean Δ (L/min)	-0.07	-0.01		0.03		0.03	
p-value*		0.216		0.044		0.033	
3072 total n	41		46		42		45
# (%) able to perform spirometry	41		46		42		45
mean Δ (L/min)	-0.01		0.05		0.08		0.07
p-value*			0.155		0.043		0.065
3100 total n	92	93	97		96	93	
# (%) able to perform spirometry	28 (30.4)	31 (33.3)	33 (34.0)		29 (30.2)	34 (36.6)	
mean Δ (L/min)	0.04	0.07	0.08		0.17	0.11	
p-value*		0.606	0.405		0.031	0.178	

Study 3069: A total of 128 (35.7%) of the patients were able to perform spirometry (67 fewer patients than those able to use the peak flow meter). The percentages of patients able to use it were similar across treatment groups. The mean changes from baseline for all the BNS treatment groups were numerically superior to that of the placebo group, with the top two doses (0.5 mg QD and 1.0 mg QD) achieving a statistically significant difference.

Study 3072: Again, all patients in this study were able to perform spirometry. The mean FEV_1 of the placebo group decreased slightly from baseline to the average of the twelve weeks of double-blind treatment. The mean FEV_1 of all the BNS groups increased slightly, with the .5 mg BID difference statistically significantly different from placebo.

Study 3100: A total of 155 (33.6%) of the patients were able to perform spirometry. The percentages of these patients were similar across treatment groups. All the BNS treatment groups were numerically superior to placebo, with the .5 mg BID treatment group mean achieving statistical significance at the .05 level. The mean changes in FEV_1 were similar across the placebo and remaining BNS groups.

APPEARS THIS WAY
ON ORIGINAL

Appendix Table 11:
Mean Changes (Adjusted for Center Effect) in FVC and corresponding $FEF_{25-75\%}$

		Placebo	.25 mg QD	.25 mg BID	.5 mg QD	.5 mg BID	1.0 mg QD	1.0 mg BID
3069	total n	92	91		83		93	
FVC	# (%) able to perform spirometry	38 (41.3)	29 (31.9)		28 (33.7)		33 (35.5)	
	mean Δ (L)	-0.04	0.05		0.06		0.04	
	p-value		0.060		0.038		0.094	
FEF_{25-75}	# (%) able to perform spirometry	38 (41.3)	29 (31.9)		28 (33.7)		33 (35.5)	
	mean Δ (L/sec)	-0.09	-0.10		0.01		-0.05	
	p-value		0.898		0.188		0.544	
3072	total n	44		47		42		45
FVC	# (%) able to perform spirometry	41		46		42		45
	mean Δ (L)	0.04		0.09		0.06		0.05
	p-value			0.292		0.607		0.751
FEF_{25-75}	# (%) able to perform spirometry	41		46		42		45
	mean Δ (L/sec)	-0.06		0.00		0.14		0.14
	p-value			0.504		0.025		0.023
3100	total n	92	93	97		96	93	
FVC	# (%) able to perform spirometry	32 (34.8)	32 (34.4)	34 (35.1)		29 (30.2)	34 (36.6)	
	mean Δ (L/min)	1.9	16.8	19.2		21.0	14.1	
	p-value		.034	.012		.010	.078	
FEF_{25-75}	# (%) able to perform spirometry	28 (30.4)	31 (33.3)	33 (34.0)		29 (30.2)	34 (36.6)	
	mean Δ (L/min)	0.04	0.07	0.08		0.17	0.11	
	p-value		0.606	0.405		0.031	0.178	

Study 3069: The mean FVC of the placebo group decreased slightly from baseline while the mean FVC of all the BNS groups increased slightly, after adjusting for center. Only the 0.5 mg QD group was statistically significantly different from placebo, at the 0.05 level. The mean $FEF_{25-75\%}$ of the top two BNS groups were numerically superior to that of placebo. Neither of the mean changes from baseline were statistically significantly different from that of placebo.

Study 3072: The mean FVC of the BNS groups were very similar, but slightly numerically superior, to the mean of the placebo group. None of the differences were statistically significant. The mean $FEF_{25-75\%}$ of the BNS groups were numerically superior to that of placebo, with the differences between .5 mg BID and 1.0 mg BID statistically significantly different from placebo.

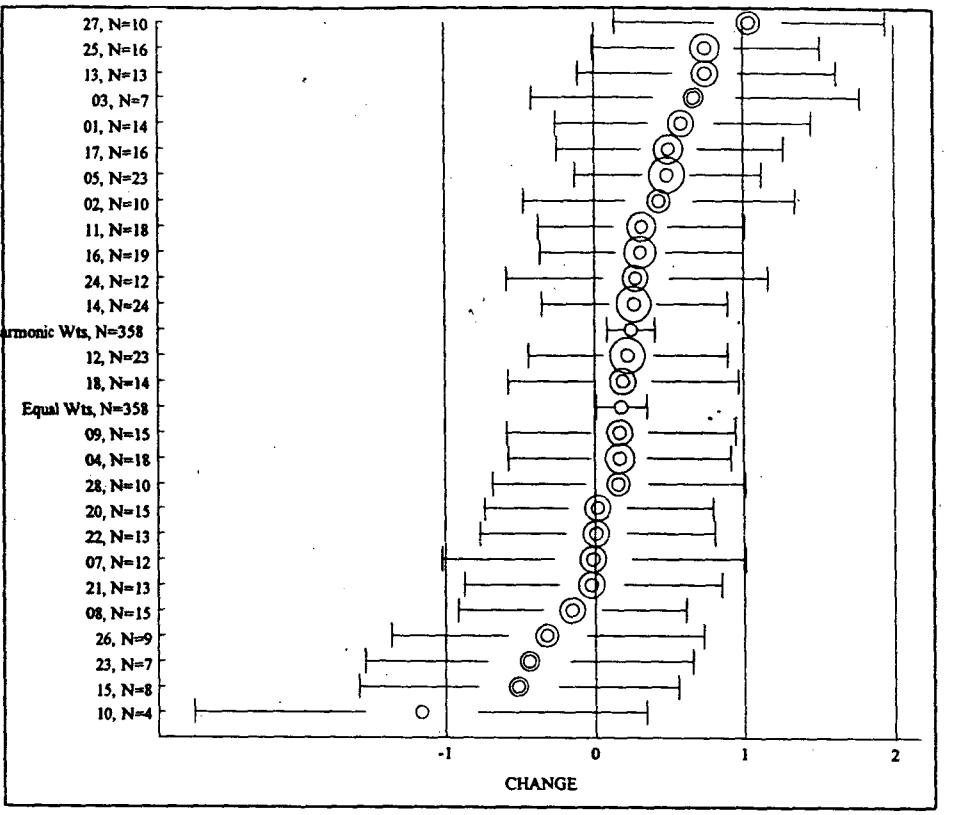
Study 3100: The mean FVC of the placebo group increased slightly from baseline (1.9 L/min) while the mean FVC of all the BNS groups increased notably (14.1 to 21.0 L/min), after adjusting for center. Only the 0.25 BID and 0.5 mg BID groups increased statistically significantly more than placebo, at the 0.05 level. The mean $FEF_{25-75\%}$ of all three BNS groups were numerically superior to that of placebo. Only the mean change from baseline of the 0.5 BID group was statistically significantly different from that of placebo.

4.4 Figures

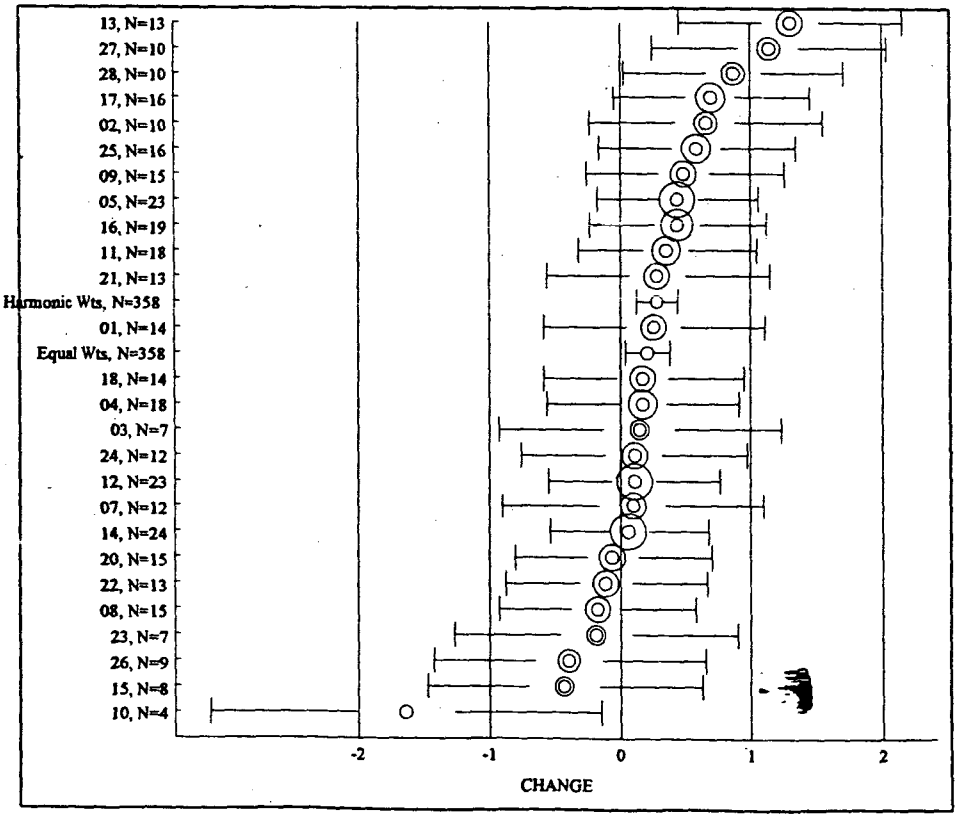
Center Effects: Figures 1-6

The following figures plot the treatment effects (and 95% confidence intervals) in each center. Numbers to the left of the y axis indicate the clinic number. Numbers to the right of the clinic number indicate the total sample size in each clinic. The size of the circle represents the size of the clinic. "Harmonic weights" is the overall treatment effect weighting all centers according to the size of the center. "Equal weights" is the overall treatment effect weighting all centers equally.

Study 3069 Daytime Symptoms: Treatment Effects by Center
(All BNS Groups vs. Placebo)

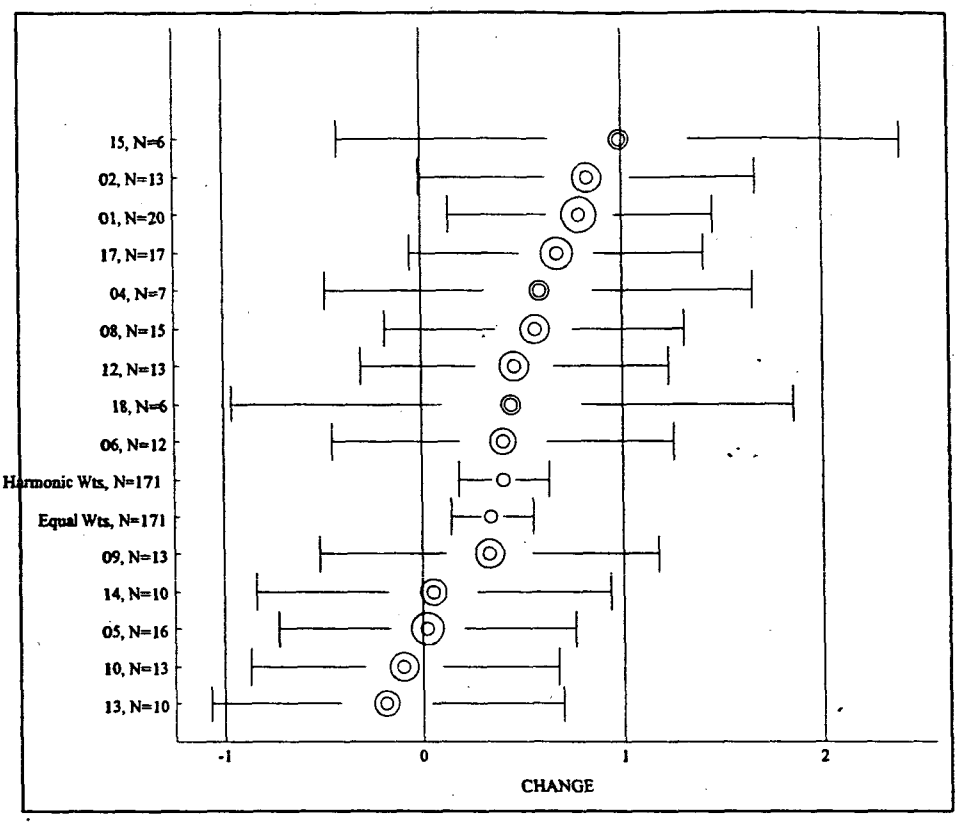


Study 3069 Daytime Symptoms: Treatment Effects by Center
(All BNS Groups vs. Placebo)

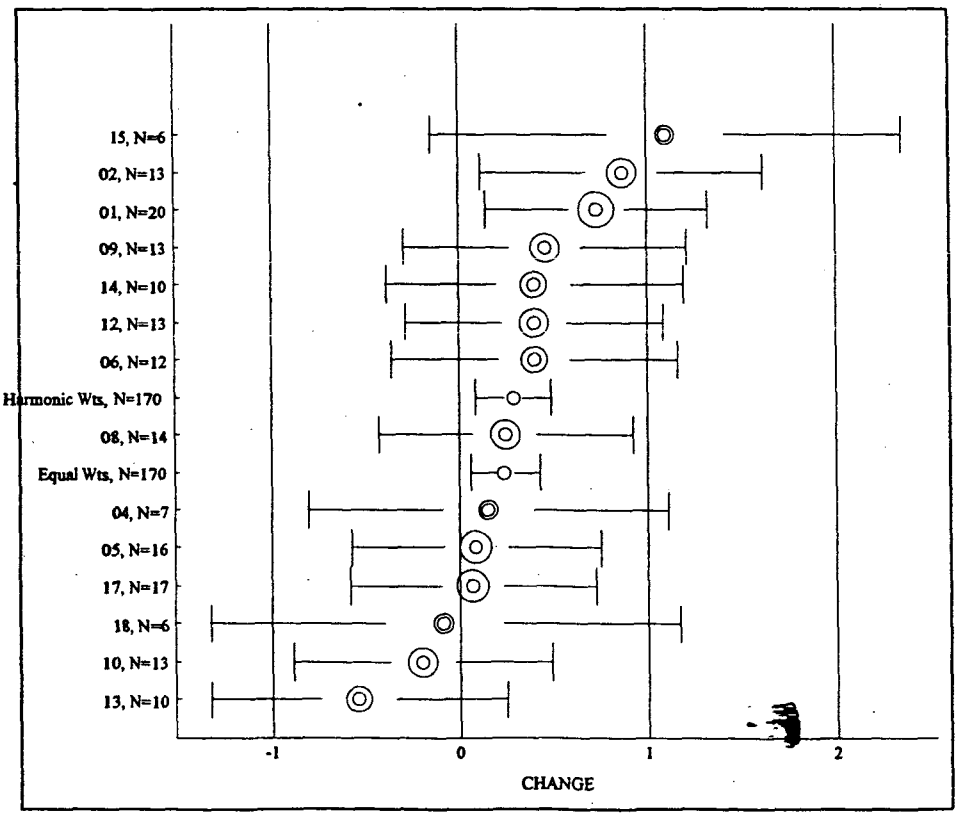


These graphs are explained on page 44.

Study 3072 Daytime Symptoms: Treatment Effects by Center
(All BNS Groups vs. Placebo)

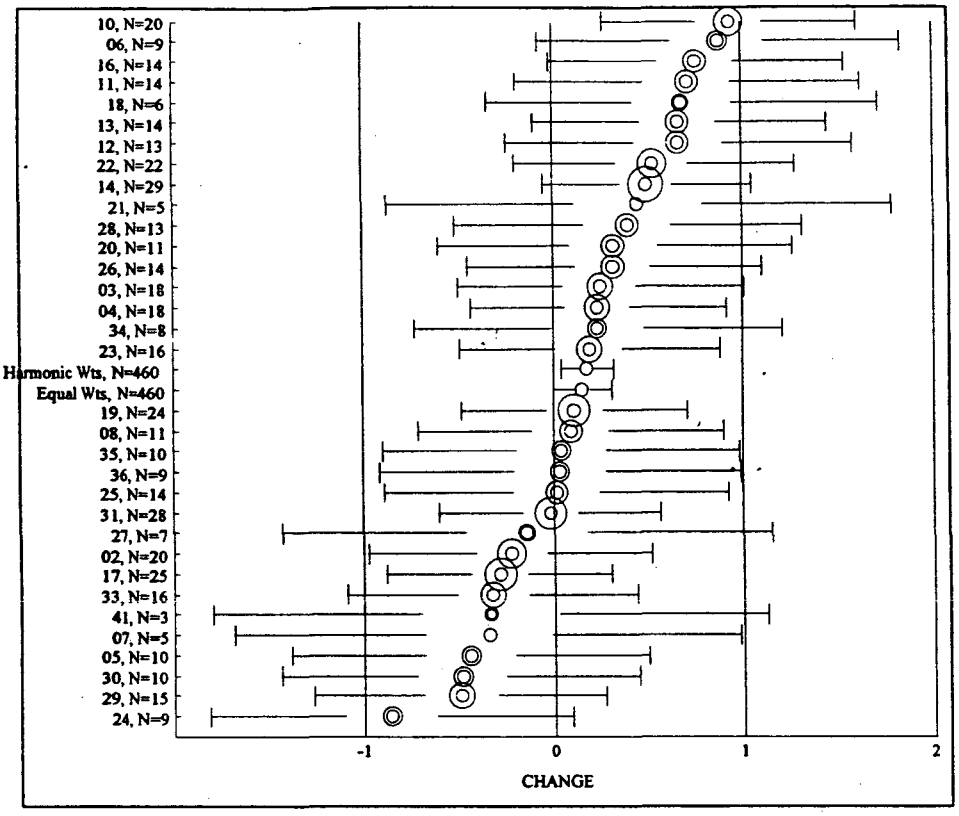


Study 3072 Nighttime Symptoms: Treatment Effects by Center
(All BNS Groups vs. Placebo)

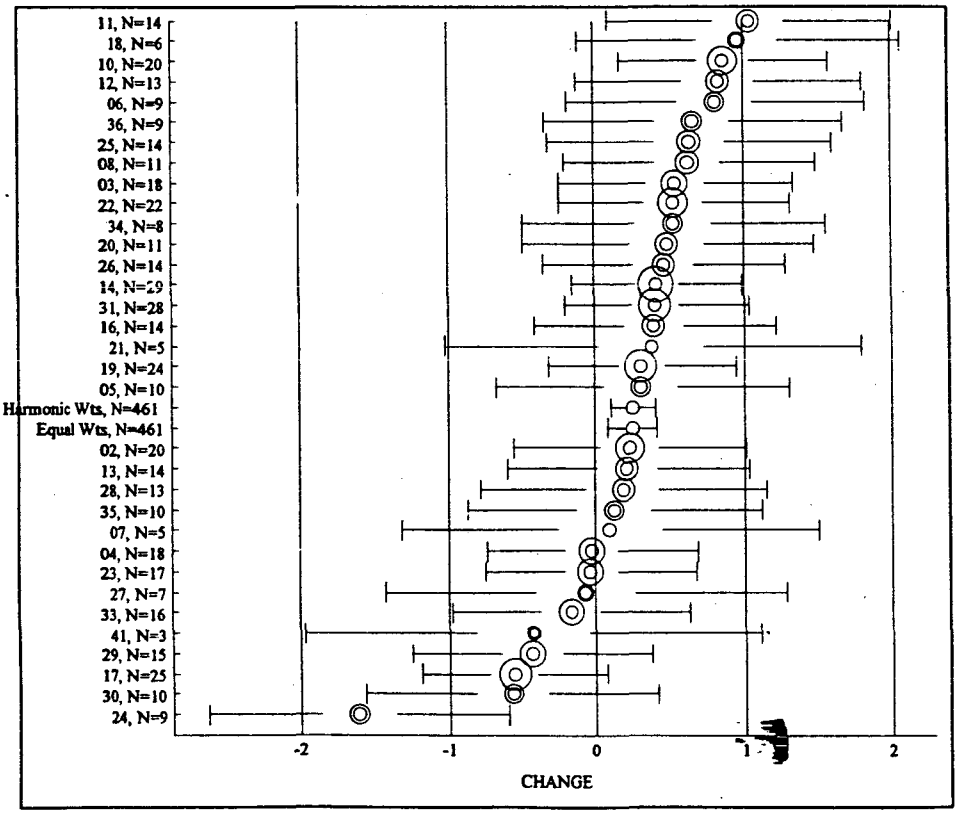


These graphs are explained on page 44.

Study 3100 Daytime Symptoms: Treatment Effects by Center
(All BNS Groups vs. Placebo)



Study 3100 Nighttime Symptoms: Treatment Effects by Center
(All BNS Groups vs. Placebo)



These graphs are explained on page 44.

Sponsor's Daytime and Nighttime Asthma Symptom Score Graphs: Figures 7-10

Figure 7: Sponsor's Graph
Study 3069 Summary of mean daytime asthma symptom scores
(All patients treated, last value carried forward)

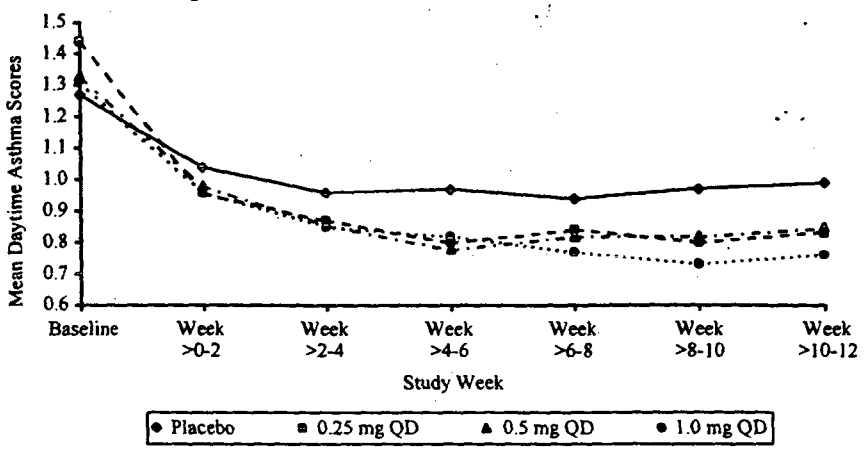
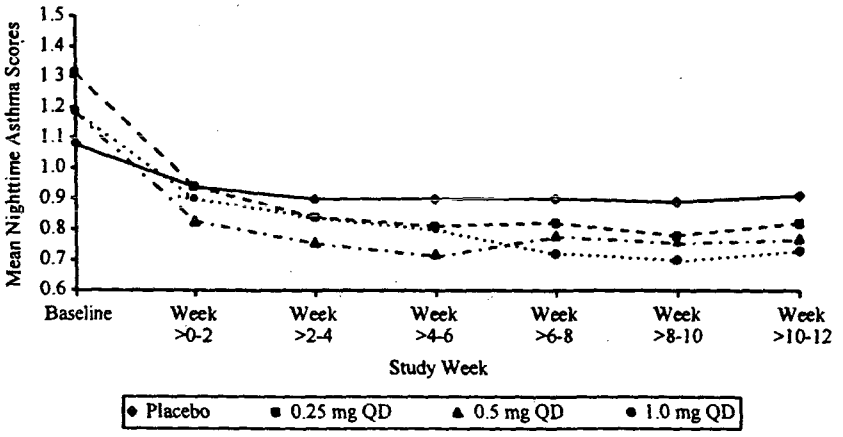


Figure 8: Sponsor's Graph
Study 3069 Summary of mean nighttime asthma symptom scores
(All patients treated, last value carried forward)



Sponsor's Graph

Study 3072 Summary of mean daytime asthma symptom scores [see Dr. Chu's review, Figure 8.3.4.4.1.1D]
Summary of mean nighttime asthma symptom scores [see Dr. Chu's review, Figure 8.3.4.4.1.1C]

Figure 9: Sponsor's Graph
Study 3100 Summary of mean daytime asthma symptom scores
(All patients treated, last value carried forward)

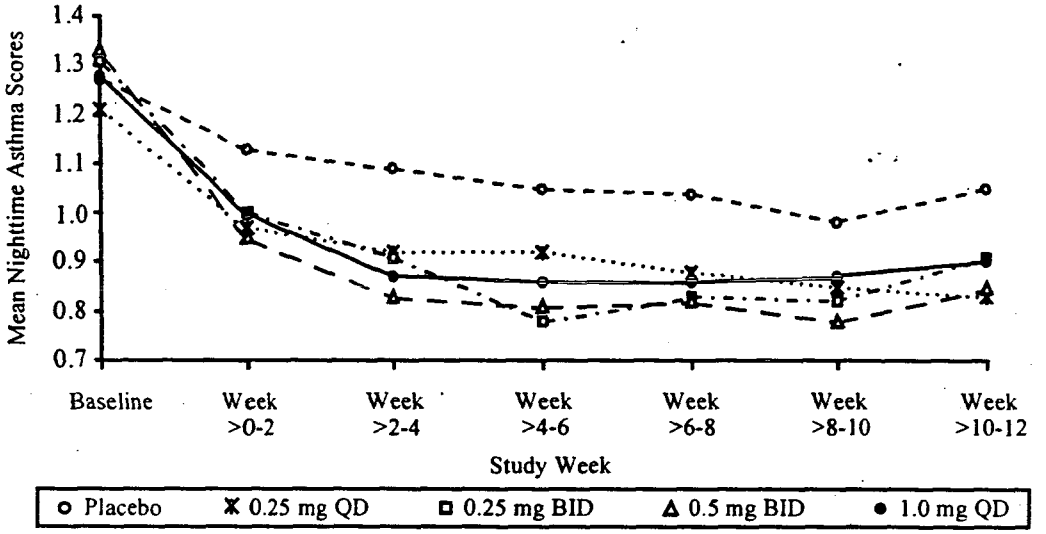
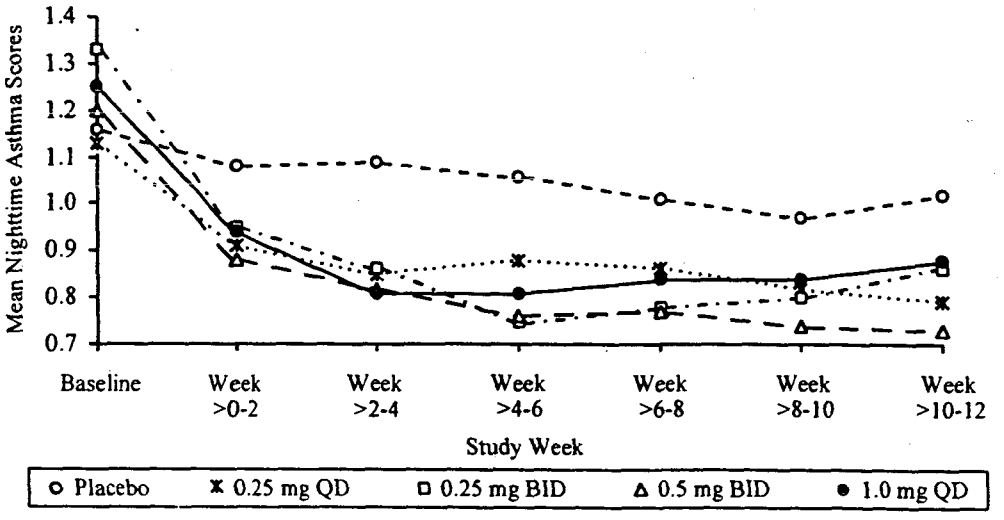


Figure 10: Sponsor's Graph
Study 3100 Summary of mean nighttime asthma symptom scores
(All patients treated, last value carried forward)



[THIS PAGE INTENTIONALLY LEFT BLANK]

Reviewer's Graphs: Figures 11-16

The following figures plot daily and weekly means of each treatment group over time for the following data:

Figure 11: Daytime Asthma Score Weeks 1-3 (daily means)
Figure 12: Nighttime Asthma Score Weeks 1-3 (daily means)
Figure 13: Daytime Asthma Score Weeks 1-12 (weekly means)
Figure 14: Nighttime Asthma Score Weeks 1-12 (weekly means)
Figure 15: Daytime Breakthrough Medication Weeks 1-12 (weekly means)
Figure 16: Nighttime Breakthrough Medication Weeks 1-12 (weekly means)

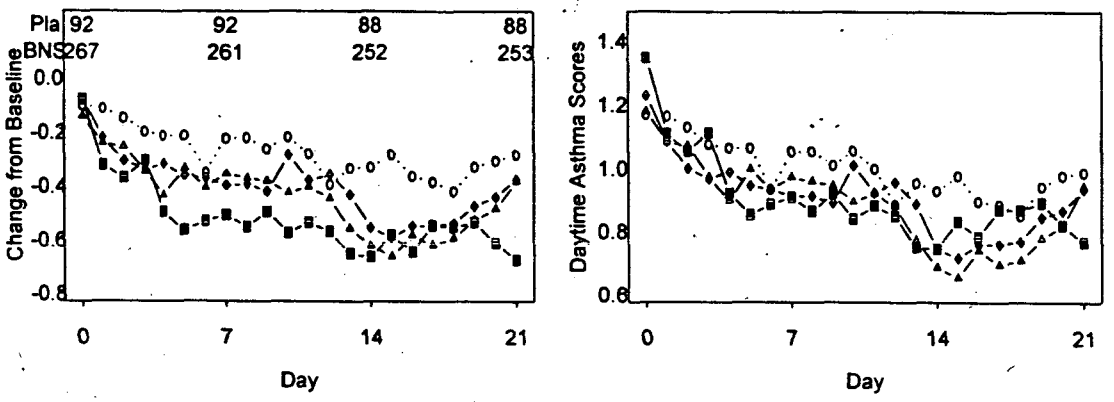
The means were calculated using all available data, unlike the sponsor's means which were calculated using last observation carried forward data. The numbers at the top of the change score graphs identify the numbers of patients remaining in the study at each time interval in each treatment group (the BNS groups were combined to accommodate space). The numbers of patients remaining at each time point in "observed values" graphs are identical to those in the "change from baseline" graphs, but not printed for the sake of simplicity. These graphs should be used in addition to the sponsor's graphs (which incorporate data carried forward for missing values) to assess onset of action and to determine if the treatment effect is sustained throughout the 12 weeks.

Figure 11: All Available Data (no data carried forward) Daily Mean Daytime Asthma Scores From Weeks 1-3

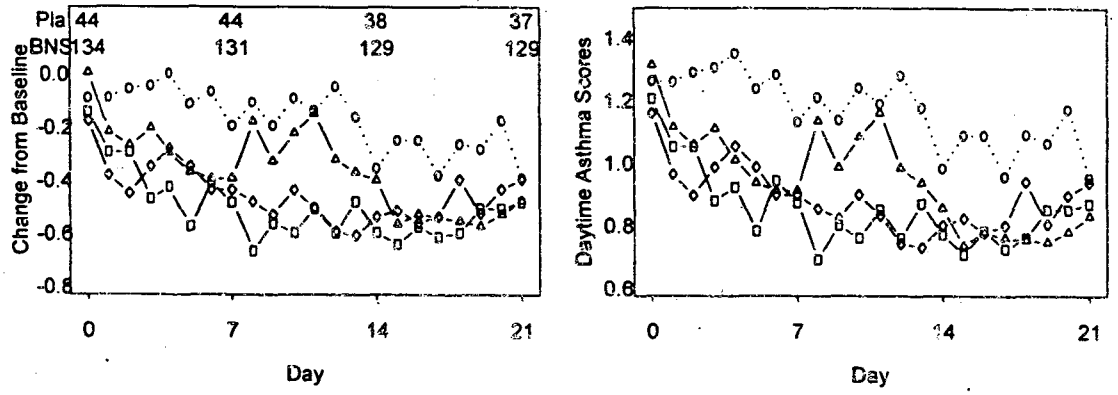
Study

Change from Baseline | Observed Values

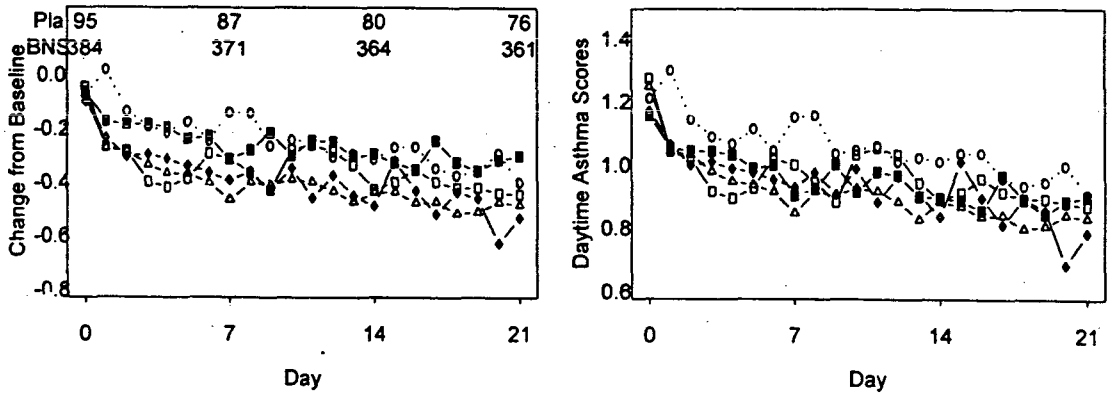
3069



3072



3100



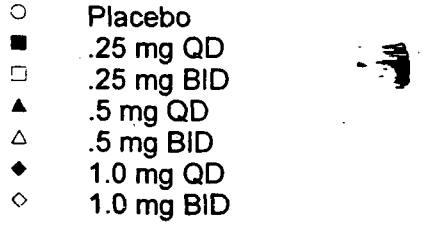


Figure 12: All Available Data (no data carried forward)
Daily Mean Nighttime Asthma Scores From Weeks 1-3

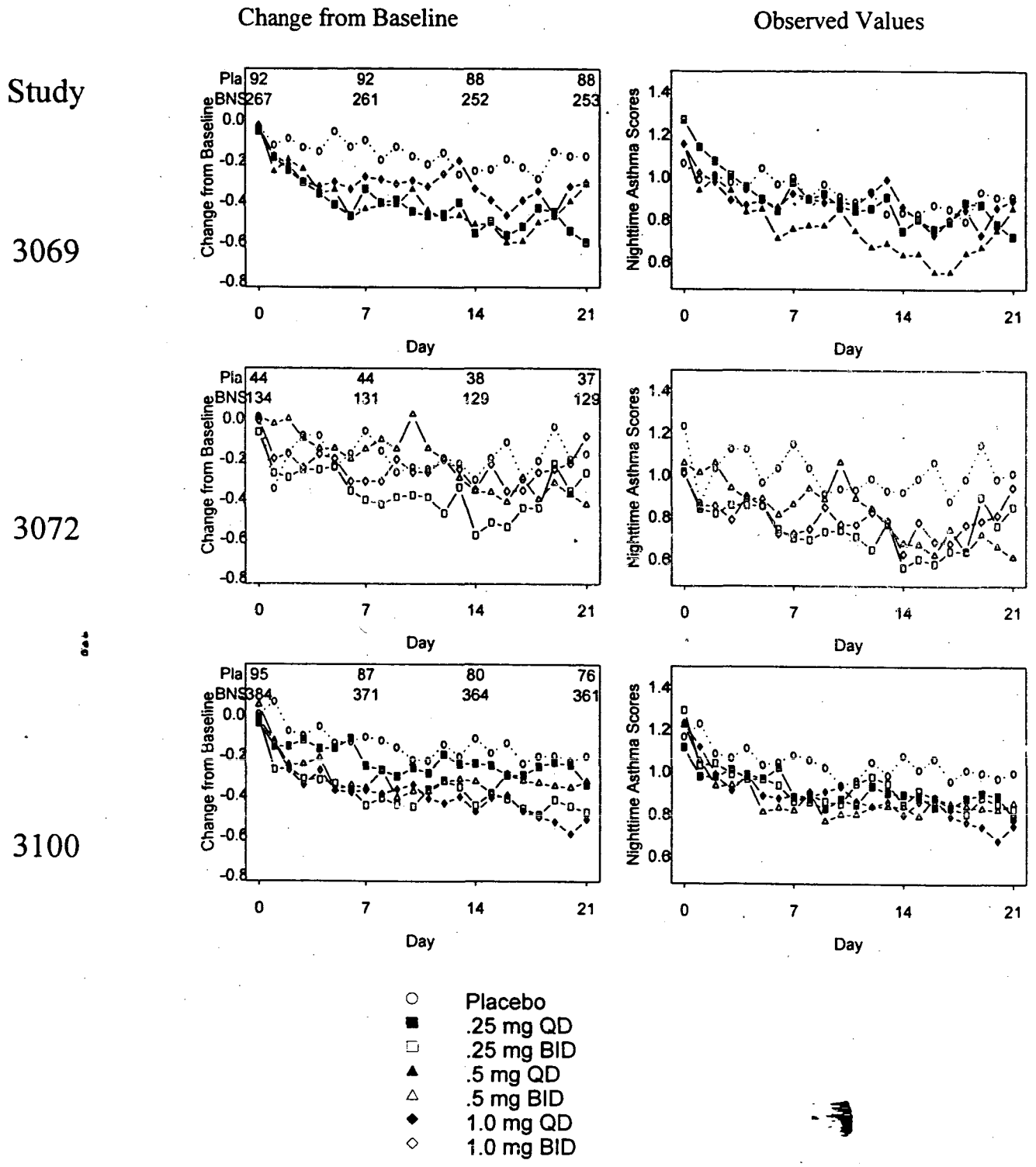


Figure 13: All Available Data (no data carried forward)
Weekly Mean Daytime Asthma Scores From Weeks 1-12

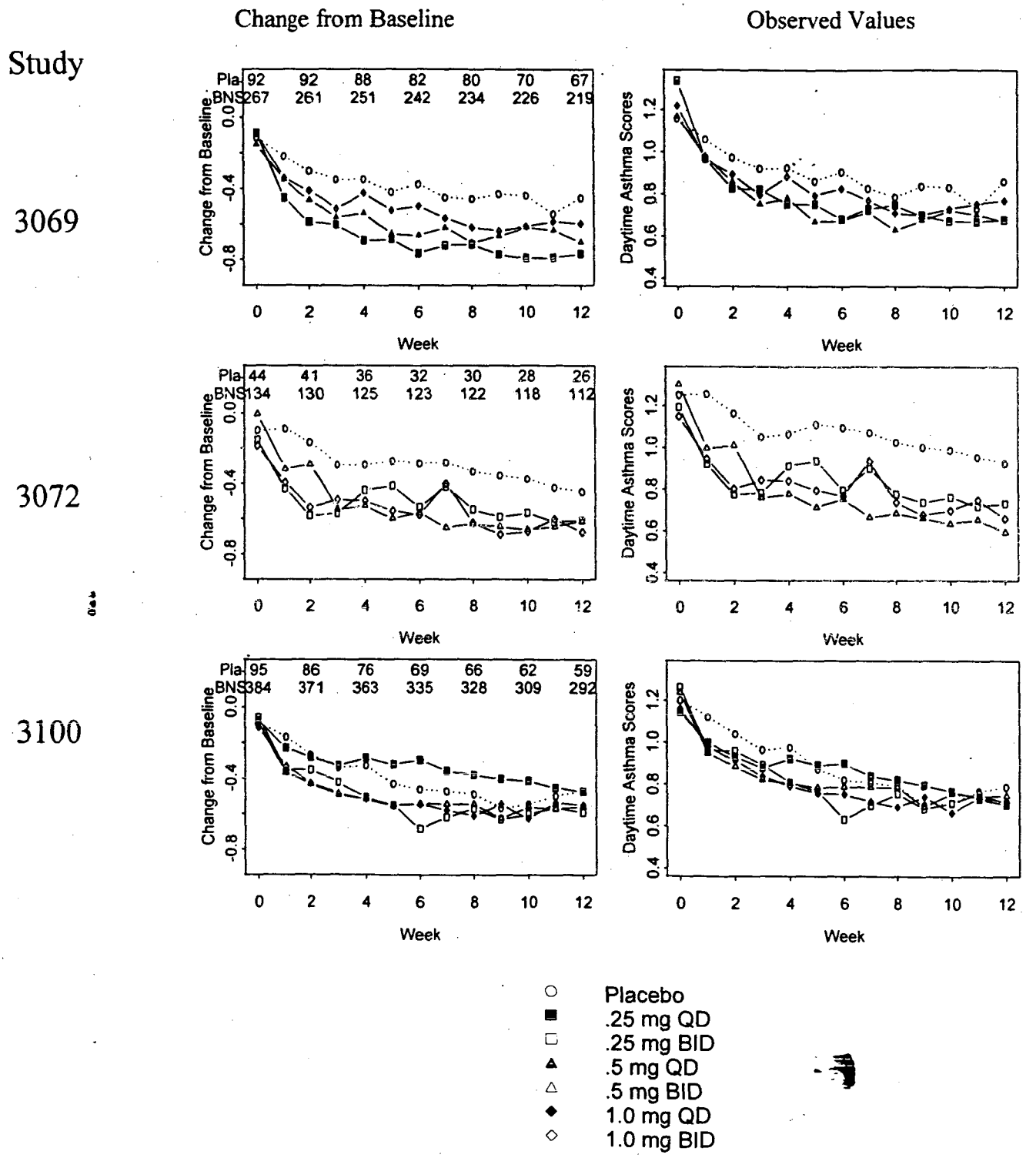


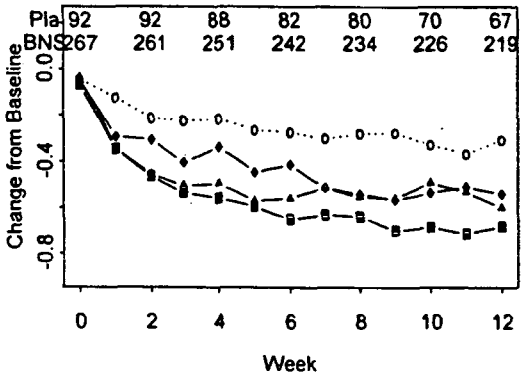
Figure 14: All Available Data (no data carried forward)
Weekly Mean Nighttime Asthma Scores From Weeks 1-12

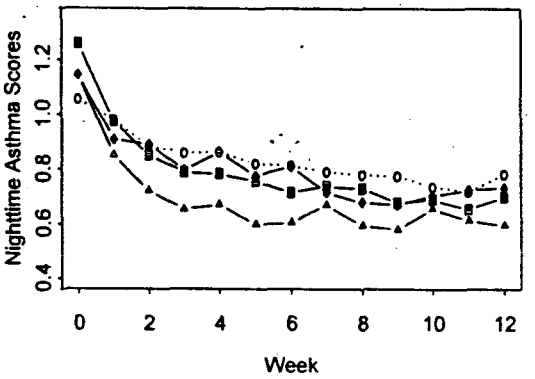
Study

Change from Baseline

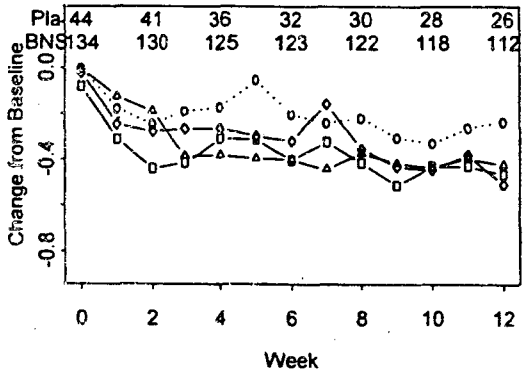
Observed Values

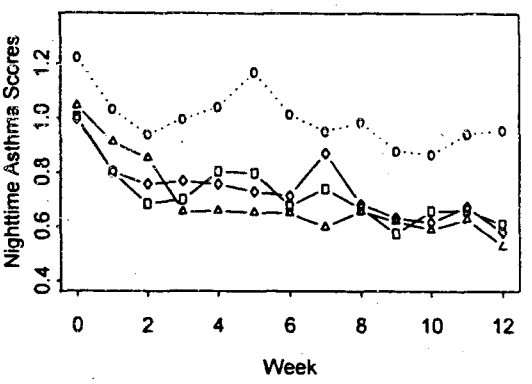
3069



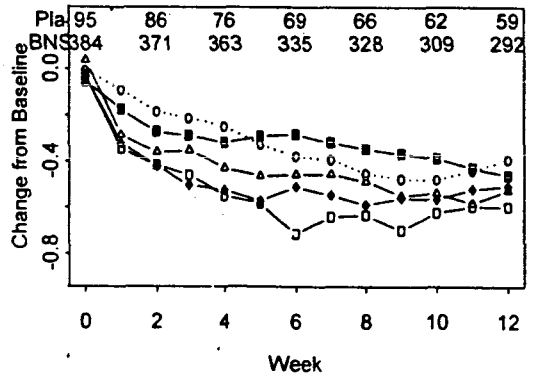


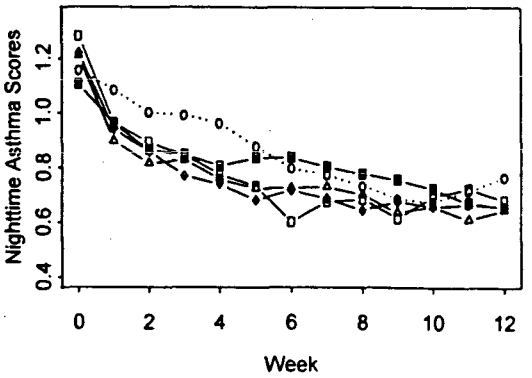
3072





3100





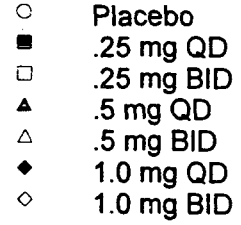
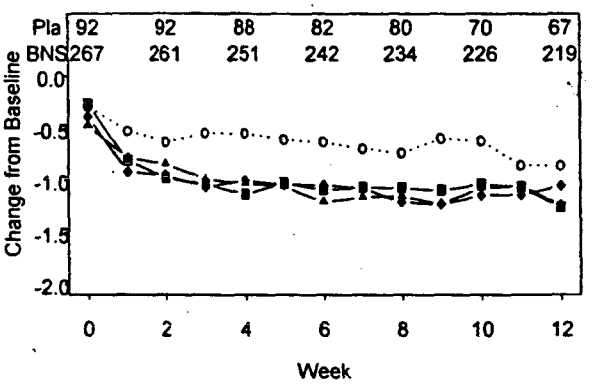


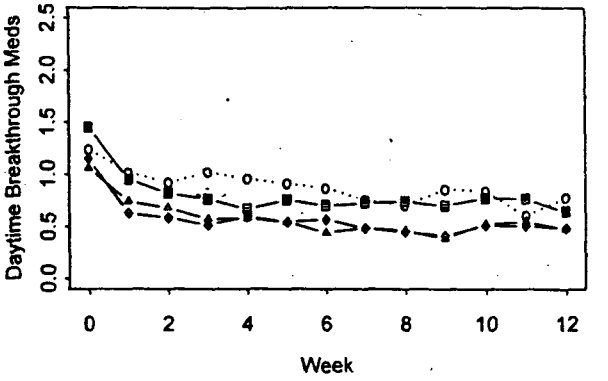
Figure 15: All Available Data (no data carried forward)
Weekly Mean Breakthrough Medication (# of doses)
From Weeks 1-12

Study

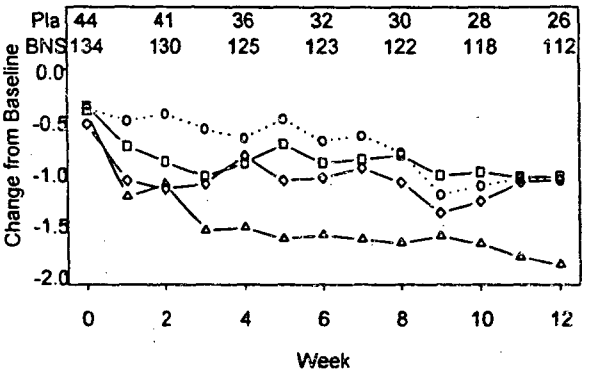
Change from Baseline | Observed Values

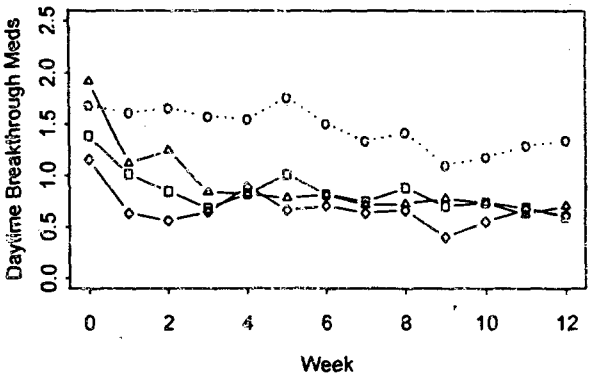
3069



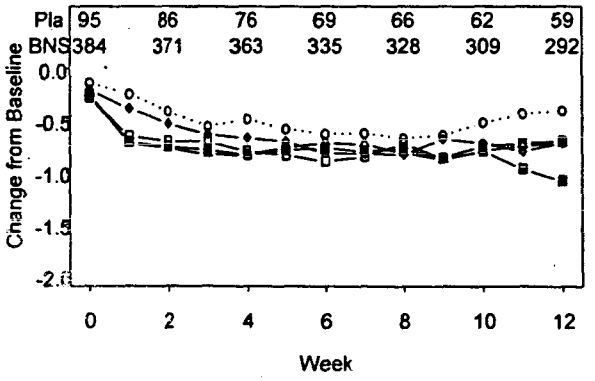


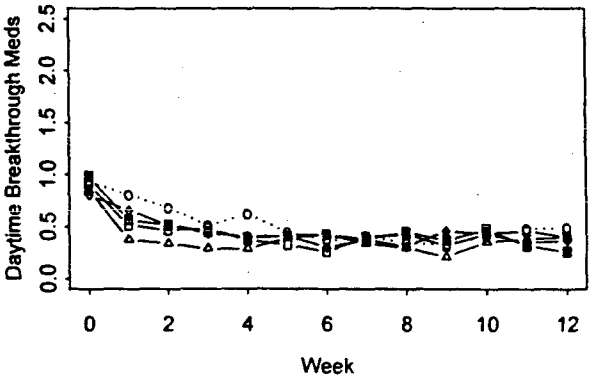
3072





3100





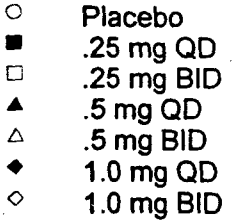
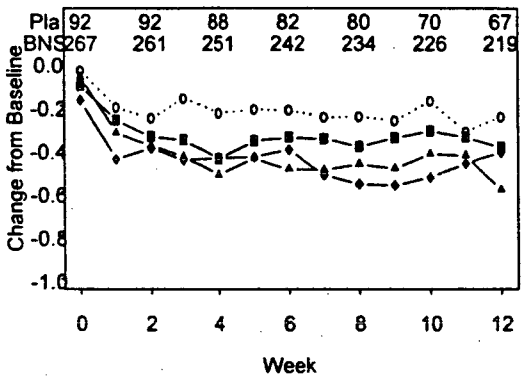


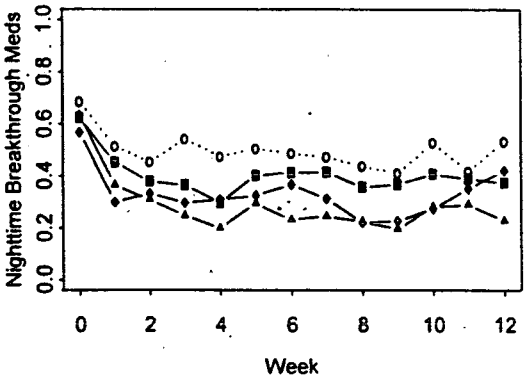
Figure 16: All Available Data (no data carried forward)
Weekly Mean Nighttime Breakthrough Medication (# of doses)
From Weeks 1-12

Study

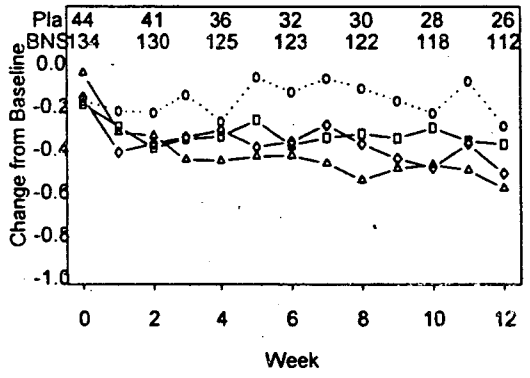
Change from Baseline | Observed Values

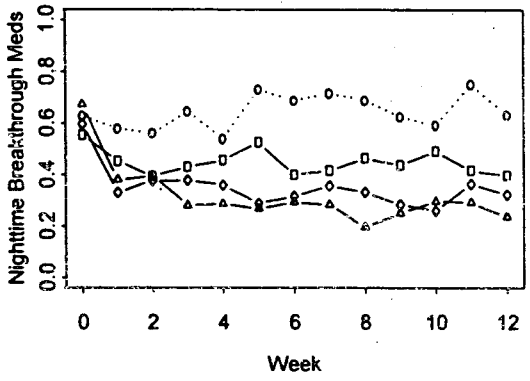
3069



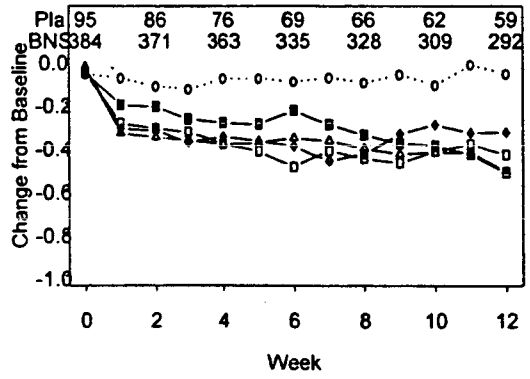


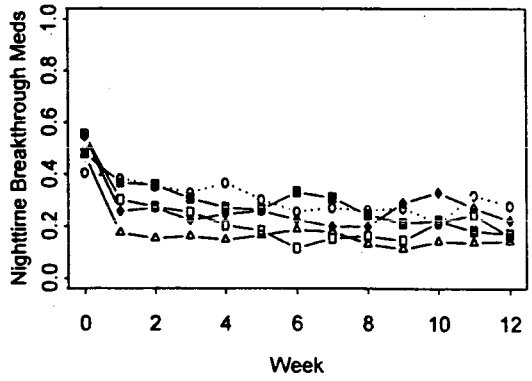
3072

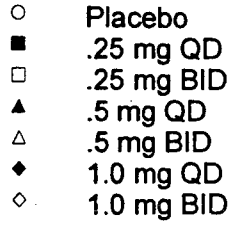




3100







Bar charts of the estimates of patient slopes (cm/year): Figure 17

(Patient #02-0234 is included in these figures using the slope calculated without the last 2 datapoints, see page27.) Note the two patients who have extreme values of slopes. BNS patient #03-0389 had an estimate slope of 28.3 cm/yr and Conventional Treatment Patient #27-0543 had an estimated slope of -1.65 cm/yr. They were not included in the analyses using the dataset called All Patients Treated #2.

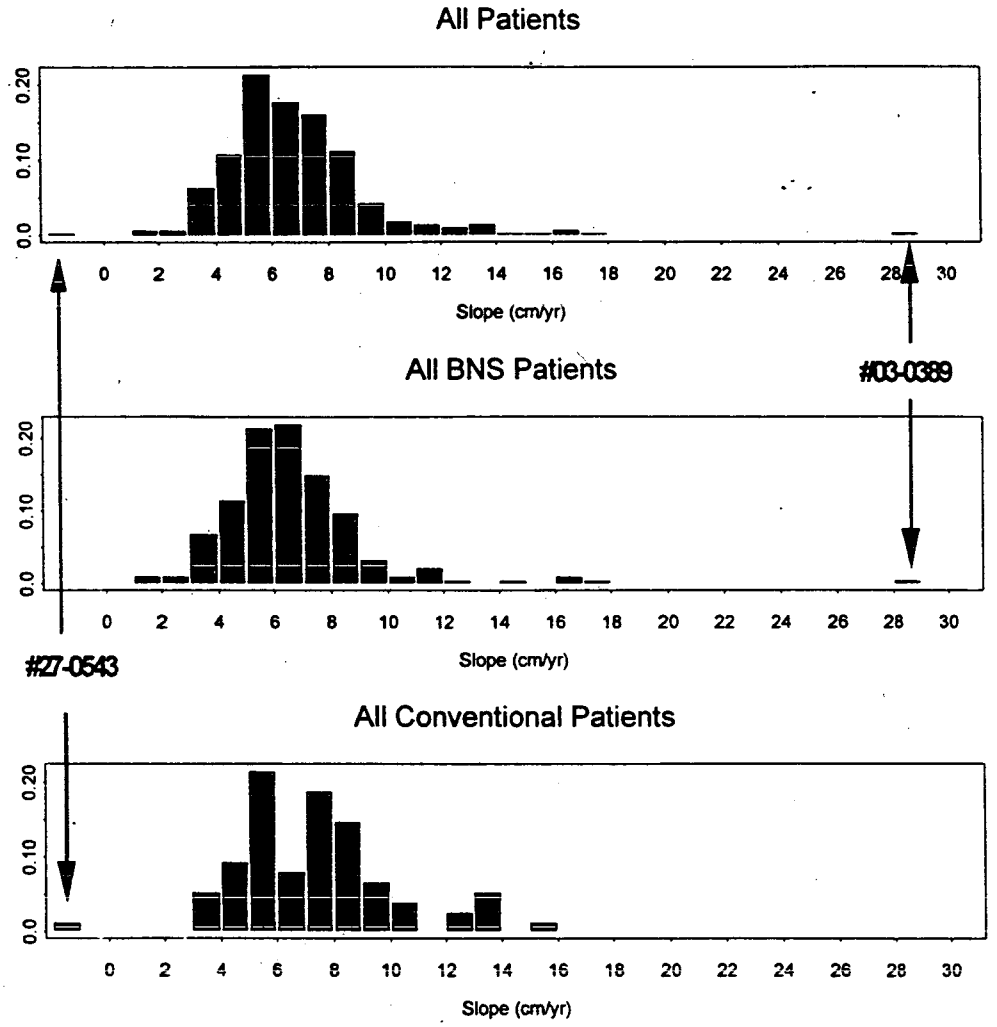
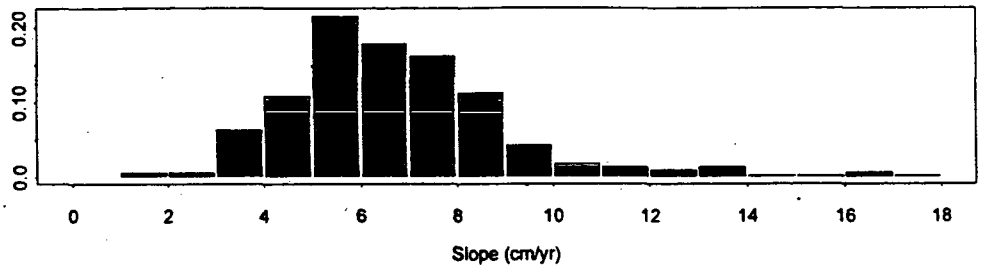
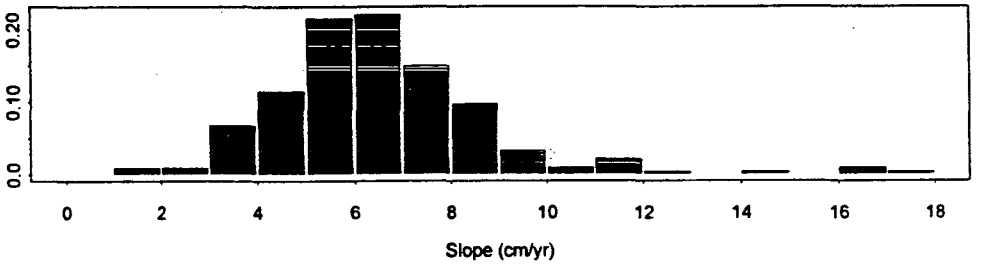


Figure 18

All Patients Except #03-0389 & #27-0543



All BNS Patients



All Conventional Patients

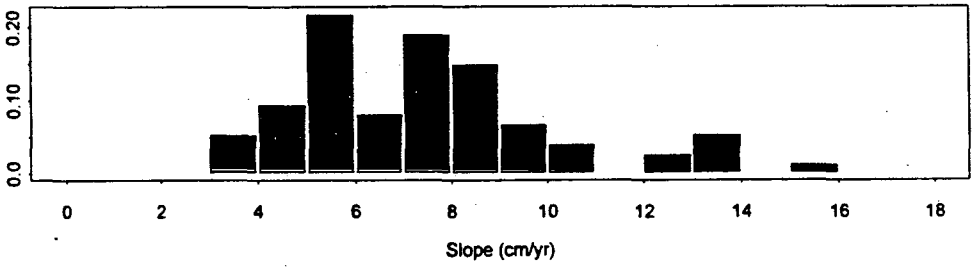


Figure 19: Mean Slopes for Each Treatment Group (comparing dropouts vs. completers)

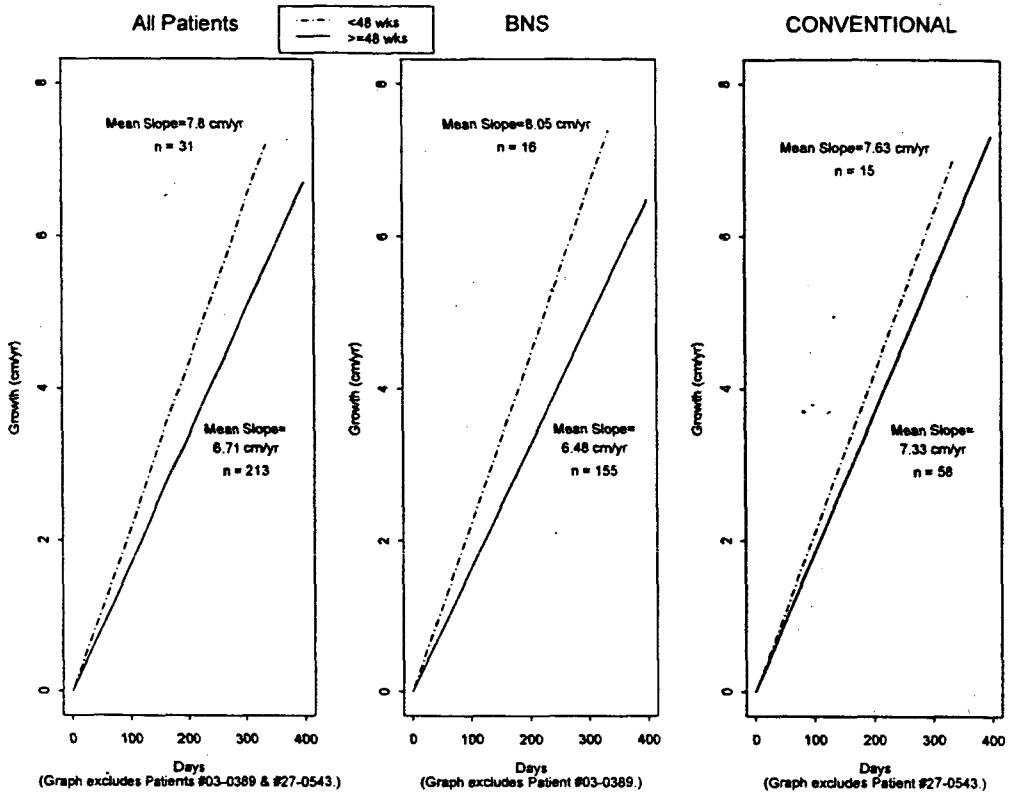
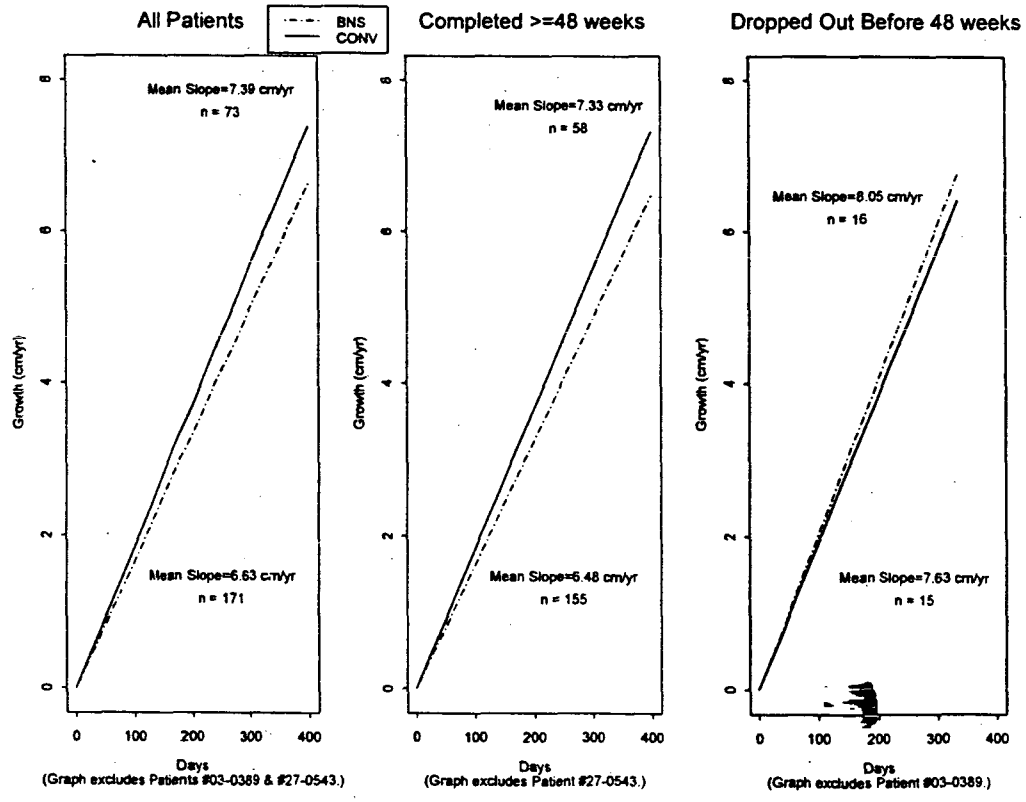


Figure 20: Mean Slopes for Dropouts and Completers (comparing treatment groups)



8 Page(s) Withheld