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APPLICATION NUMBER:

20-929

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: FEB 4 1999

NDA#:	**20-929**
Applicant:	**Astra USA, Inc.**
Name of Drug:	**Pulmicort Respules (budesonide nebulizing suspension)**
Indication:	**Asthma**
Documents Reviewed:	**7-18-97, 7-25-97 IND 044535 (electronic data and study reports submitted to IND 44, 535), 11/20/97 NDA 20-929; 8-7-98 (major amendment)**
Statistical Reviewer:	**Barbara Elashoff, M.S.**
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Summary

This review explores the quality and the reliability of the growth velocity results of Studies 3069b, 3072b and 3100b. Study 3069b compared budesonide to a control group of non-corticosteroid asthma therapy, whereas Studies 3072b and 3100b compared budesonide to a control group (that included a variety of inhaled corticosteroids). As stated in the previous review of the clinical study report for Study 3069b submitted to the original NDA, the results of Study 3069b provide some evidence that BNS affects growth velocity in children. However, the results should be viewed with caution due to problems with study design (open-label, patient self-selection, no washout period between two phases of the study), study conduct (high, differential dropout rates and oral corticosteroid use) and data analysis (*post-hoc* selection of patients, endpoint, and method of analysis). The results of Studies 3072b and 3100b appear to suggest a beneficial effect of BNS on growth velocity over the control group (inhaled corticosteroids other than BNS). However, in addition to the problems of study design and conduct described above, the control groups used in Studies 3072b and 3100b were not adequate. The control group patients were treated with a variety of different inhaled steroids and the procedures for dose reduction were required only for the BNS arm, not the control arm. The direction and magnitude of the bias introduced by the problems associated with study design and conduct is unknown. Therefore, the estimates of the differences in mean growth velocities from these studies are unreliable and should not be in the label.

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1 Background and Study Design

The sponsor submitted two studies to this supplement, Studies 3072b and 3100b (see Figure 1 below). Studies 3069b (submitted to the original NDA), 3072b, and 3100b were 52-week open-label extensions of Studies 3069, 3072 and 3100, respectively (see Statistical Review and Evaluation NDA 20-929, May 6, 1998, for a review of Studies 3069, 3069b, 3072, and 3100). These long-term open-label extension studies were designed to assess safety factors of budesonide nebulizing suspension (BNS). One of the safety endpoints was growth velocity. As reported in the clinical and statistical reviews of the original application, Study 3069b found a statistically significantly lower mean growth velocity in the budesonide treated patients compared with the growth velocity of patients who received alternative, non-steroidal therapies. The sponsor's results in the current submission are somewhat inconsistent with this finding, suggesting a beneficial effect on growth in comparisons with patients who received a variety of alternative therapies, including treatment with other inhaled glucocorticosteroids. This review summarizes the results of these three open-label safety extension studies. (Study 3069b is included in this review for comparison of results.)

Figure 1

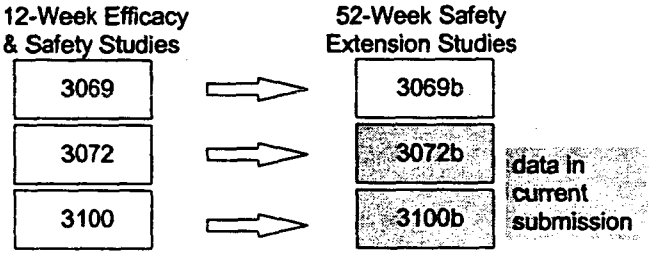


Table 1: Summary of Studies

	Study Number		
	04-3069b	04-3072b	04-3100b
Number Randomized to Open-label extension	272	91	307
Dates Conducted	10/94-12/96	8/95-11/97	11/95- 6/97
BNS starting dose	0.5 mg QD	0.5 mg BID	0.5 mg QD
Control Group: included Beta2-agonists, methylxanthines, inhaled non-steroidal anti-inflammatory agents	no inhaled glucocorticosteroids allowed	inhaled gluco-corticosteroids allowed	inhaled gluco-corticosteroids allowed
Age Range	9 months to 9 years	4-9 years	9 months to 9 years
Severity of Asthma	Non-steroid dependent asthmatic patients	Inhaled steroid dependent asthmatic patients	Mild to moderate asthmatic patients
Treatment Period	52 weeks	52 weeks	52 weeks
Number of Investigators/Sites	28 investigators at 26 sites	18 investigators at 17 sites	38 investigators at 38 sites
Asthma Medications allowed prior to randomization of the double-blind period	Bronchodilators, cromolyn sodium, nedocromil sodium	Inhaled steroids (required), bronchodilators, cromolyn sodium, nedocromil sodium	Inhaled steroids (optional), bronchodilators, cromolyn sodium, nedocromil sodium

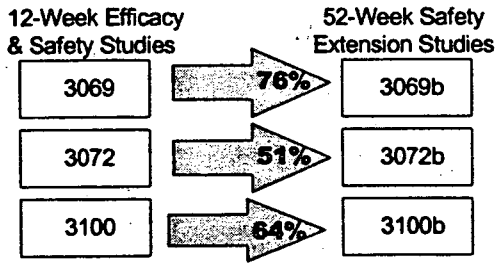
For most patients, entry into the open label study immediately followed their completion of the double-blind phase. About 40% of the patients in Studies 3072b and 3100b had already completed the double-blind phase and were called back for entry into the open-label phase.[1] Patients entering the open label study were re-randomized (2:1) to either BNS

[1] In Study 3069, some patients may have had a period of a few months in between phases due to an early protocol that did not allow patients who dropped out of the double-blind phase to continue in the open-label phase. An amendment to the protocol changed the rule and allowed dropouts to enter the open-label phase. Some of the patients who had dropped out before the amendment was approved were called back and re-entered the study, in the open-label phase. (The sponsor did not state to how many patients this applied.) In Studies 3072 and 3100, the original design did not include an open-label treatment phase. Amendment #1 added the

or Conventional Treatment (CT). The "conventional treatment" arm in all of the studies included Beta2-agonists, methylxanthines and inhaled non-steroidal anti-inflammatory agents. The CT patients in Studies 3072b and 3100b were also allowed to use inhaled glucocorticosteroids. (It should be noted that there is evidence that, as a class, inhaled glucocorticosteroids slow growth velocity.) Patients randomized to BNS received a starting dose of .5 mg QD in Studies 3069b and 3100b and .5 mg BID in Study 3072b. In all studies, the protocol stated that at every visit the investigators should address the issue of reducing BNS patients to lower doses. The protocols of Studies 3072b and 3100b did not state that the investigators should try to reduce the levels of inhaled corticosteroids for the CT patients.

Continuing into the open-label extension phase was optional for patients. The percentage of patients who continued was greatest in Study 3069 (76%) and least in Study 3072 (51%).

Figure 2



After randomization, about 2-10% of the patients discontinued before the second visit (see Table 2). There were differences in percentages across treatment groups with a higher percentage of these early discontinuations among the patients randomized to CT. (Dropout rates are discussed in detail in Appendix, page 18).

Table 2: Discontinuation Rates Before Second Visit

	Study 3069b	Study 3072b	Study 3100b
CT	6/90 (7)	3/30 (10)	10/103 (10)
BNS	3/182 (2)	1/61 (2)	4/204 (2)

Reviewer Comment

As is standard practice, these safety studies measured a number of safety endpoints, including: adverse events, laboratory values, vital signs, HPA-axis, oral and nasal fungal cultures, skeletal age, and growth velocity. The protocols did not select a "primary" safety endpoint.

About 60% of the patients started the open-label phase with no washout period after the double-blind phase. Since some of these patients were taking BNS during the double-blind phase while others were taking placebo, any effects of the double-blind treatment medication may have carried over into the open-label phase.

Randomization is expected to balance patients with baseline characteristics (known and unknown) across treatment groups. However, it may not have been effective in these open-label studies. It appears as though the patient populations were somewhat "self-selected", due to differences in early discontinuations. Patients with less than two datapoints cannot be evaluated in this trial, therefore these early discontinuations may have changed the population of evaluable patients.

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open-label-extension to the studies, allowing those patients who retrospectively or prospectively successfully completed the 12-week, double-blind treatment phase or discontinued due to worsening of asthma requiring oral corticosteroids to enter open-label. For those patients who had completed the double-blind treatment phase or had been discontinued due to worsening of asthma requiring oral corticosteroids at the time of the amendment, a new Visit 6A was implemented. As a consequence, 46% of the patients in Study 3072 (49% of the budesonide patients; 40% of the CT asthma patients) and 43 % of the patients in Study 3100 (43% of the budesonide patients; 44% of the CT asthma patients) had already completed the double-blind treatment phase prior to the implementation of the amendments, and thus had a time lapse between the end of the double-blind phase and the beginning of the open-label phase, during which they were treated with asthma medications (including inhaled corticosteroids) per the judgment of their physicians.

The patient populations in these studies were not random samples of asthma patients. They were self-selected subsets of patients from three completed trials. Therefore these studies do not represent standard adequate and well-controlled randomized clinical trials.

In addition, the control arms were not well-specified. The patients were treated with a variety of different inhaled corticosteroids, starting at doses that were not specified in the protocol.

The open-label nature of these studies may also have contributed to differences in the way the investigators treated the patients. The dose of the inhaled corticosteroids for the BNS patients was adjusted to meet the individual patient needs. The protocol emphasized that the investigator should attempt to lower the dose at every visit. The investigator was not instructed to do the same for the patients on inhaled corticosteroids who were randomized to CT. To some extent this may have biased the results in favor of budesonide. In addition, the unblinded investigators may have added rescue medication to the CT patients' treatment regimen more liberally.

As these were open-label studies, the observed results (efficacy and safety) were subject to bias introduced by the investigators and patients. The subjective efficacy endpoints, such as asthma symptom scores, were especially biased due to the unblinded nature of the study. The results of the efficacy endpoints are discussed in the Appendix, page 14.

2 Proposed Label

The sponsor proposed the following wording for the label regarding [redacted]

[redacted]

Reviewer Comment

The sponsor has proposed to include [redacted] in the labeling. These trials are of uneven quality and difficult to interpret. The two studies submitted in this amendment (Studies 3072b and 3100b) were not well-controlled and did not include representative samples of children with asthma. The studies were safety studies, with no pre-specified "primary" safety endpoint. The effects of multiple biases on these post-hoc estimates are unknown and therefore, it is impossible to determine the accuracy of the results. The sponsor attempts to maintain some scientific equipoise by stating that the [redacted] This review maintains that [redacted] in the label implies an acceptance by the Agency of the studies as "adequate and well-controlled", and of the estimates as accurate. Therefore, [redacted] should not be included in the label. The following sections explore these issues and discuss the effects they may have had on the reported results.

3 Results

The reported results of the three studies are difficult to interpret. Study 3069b suggested that BNS affected the growth velocity more than did the conventional, non-steroidal treatment, while in Studies 3100b and 3072b children in the BNS treatment groups appear to have grown faster than children who were receiving "conventional" treatments (including inhaled steroids). Other factors (design, conduct and analysis) that complicate the interpretation of study results include: unblinded treatments, lack of data on baseline growth velocity, self-selection into the study, previous use of study drug, differential discontinuation, selection of patients for analysis and differential prednisone use. These issues are described in this review.

3.1 Demographics

Table 2 below includes information describing the demographic characteristics of treatment groups in each of the three studies. It is generally appreciated that the growth velocity of children is markedly different in different age groups. Therefore the number and percent of children in each age group for each treatment group becomes an important factor in assessing the results of growth studies. It appears from these data that, at baseline, the children in Studies 3069, 3072b 3100b were equally distributed by age across treatment groups. However, Study 3072b was different from the other two studies in that no children 9 months to 4 years of age (a period of relatively high growth) were included in the trial, (see Appendix Figure A2, page 13).

Table 3: Demographics Characteristics by Treatment and Study*

	3069b		3072b		3100b	
	CT	BNS	CT	BNS	CT	BNS
n randomized	90	182	30	61	103	204
n included in analyses	74	168	26	59	87	193
Age Range	1-9 years	8 months-9 years	4-9 years	4-9 years	1-9 years	1-9years
Mean age (months)	61	59	87	82	60	56
# (%) 0-1 yrs	8 (11)	13 (8)	0	0	10 (11)	18 (9)
# (%) 2-3 yrs	15 (20)	43 (26)	0	0	20 (23)	58 (30)
# (%) 4-9 yrs	51 (69)	112 (67)	26 (100)	59 (100)	57 (66)	117 (61)
Race # (%) Caucasian	51 (69)	126 (75)	21 (81)	51 (86)	64 (74)	160 (83)
Gender # (%) Male	49 (66)	114 (68)	14 (54)	37 (63)	58 (67)	118 (61)

* The numbers and means in this table refer to the cohort of patients who were included in the reviewer's ITT analyses (see page 7).

Reviewer Comment

Although two of the trials (Studies 3069b and 3100b) studied patients who were apparently equally distributed by age and gender across treatment groups, there are a number of questions that remain that make it difficult to make cross-study comparisons. One of the most important factors related to growth studies is baseline growth velocity. The sponsor did not include a baseline period in which to measure the growth velocity of patients in any of these studies and therefore, did not have the data needed to 1) know how similar the patients were at baseline, or 2) analyze the influence of this important variable on study results.

By the end of the 52-weeks, some of the patients were ten years old. It is possible that the patients had entered puberty. The sponsor did not discuss puberty status in the study report and no data were provided regarding puberty status.

3.2 Study Conduct

Compliance to study procedures was assessed for each patient at each visit in Studies 3069b and 3072b. With the exception of the Study 3069b CT group, the percent of compliant patients over the 52 weeks was high (>80%, see Table 4 below).

Study drug compliance was assessed by the investigator at all clinic visits after Visit 6 (or 6A). The patients were instructed to return all unused study drug and nebulizers at each clinic visit. The investigator then inventoried the log and the returned study drug. In all three studies, compliance to budesonide study medication was high (>80%, see Table 4 below).

Studies 3069b, 3072b and 3100b allowed the investigators to adjust the dose of budesonide to the individual patient's needs. Only 14-18% of the patients in the studies had the dose adjusted down from the initial starting dose and remained at the lower dose level. In all three studies, the average total daily dose was in the range of the starting dose for the study.

The percentages of dropouts in Studies 3069b and 3100b were high and different across treatment groups (see Table 4 below.) In Studies 3069b and 3100b, much higher percentages of patients in the CT groups dropped out. However, in Study 3072b lower and equal proportions of patients failed to complete the studies.

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 percentage of patients who used oral corticosteroids was high (>50%) and only slightly different between the treatment groups in all three studies. The Appendix pages 15-17 discusses differences in prednisone use across treatment groups for patients who completed at least 60 days of the studies. Among these patients, the differences across treatment groups are greater.

Table 4: Sponsor's Summary of Results

	3069b		3072b		3100b	
	CT	BNS	CT	BNS	CT	BNS
n randomized	90	182	30	61	103	204
Compliance to Study Procedures[1]	60-80%	77-90%	80-90%	84-95%	Not Available[5]	
Compliance to BNS[2]		82-93%		87-97%		84-93%
Mean total daily dose of BNS (mg)		0.52-0.54		0.88-1.0		0.5
# (%) who titrated down[3]		27 (15)		11 (18)		28 (14)
# (%) dropout[4]	31 (34)	24 (13)	4 (13)	7 (12)	29 (28)	26 (13)
# (%) used oral corticosteroids	48 (53)	84 (46)	19 (63)	34 (56)	56 (54)	105 (51)

1 The percent of patients in compliance to study procedures at the time of each visit was calculated. The range given in the table is the range of percentages over all the visits.
2 Compliance to BNS refers to compliance with administration of BNS study medication.
3 Patients who were titrated down refers to patients who were reduced from the initial starting dose of BNS and stayed below it for the remainder of the study.
4 Dropouts refers to patients who dropped out of the study before 300 days, or 10 months.
5 The study report did not include these data.

Reviewer Comment

Compliance to study drug was only measured in the BNS treatment group, not the control arm. This is another indication that the studies were not really "controlled trials" in the traditional sense.

High and differential dropout and prednisone use may have affected the estimate of the treatment differences. Among the patients who were included in the analyses, there were differences in percentages of patients using prednisone and number of days use across treatment arms. This is discussed further in the Appendix page 15.

3.3 Growth Velocity Results

3.3.1 Sponsor's Analyses

The sponsor performed analyses on the change in the standardized percent predicted height scores, or "z-scores". The z-scores are defined in the Appendix page13. The change in the z-scores was the dependent variable in an ANOVA with center and treatment as factors and baseline z-score as a covariate. The p-value in the table below is from the ANOVA on z-scores. The means the sponsor [redacted] presented in the table below) are the means from a different ANOVA on the change from baseline height (not z-score), adjusted for center and baseline height. Table 5 below is a summary of the sponsor's results.

Table 5: Sponsor's Growth Velocity Analyses

	3069b		3072b		3100b	
	CT	BNS	CT	BNS	CT	BNS
n used in analysis	58	151	25	47	72	167
ANOVA on height measurements:						
-Mean Growth Velocity (cm/yr)	7.39	6.55	4.97	5.68	6.21	6.96
-Standard deviation	2.51	2.08	2.00	1.71	2.43	2.34
-Difference in growth velocities (cm/yr)	0.84		-0.71		-0.75	
p-value from ANOVA on z-scores	0.003		0.155		0.113	

In calculating these estimates, the sponsor deleted patients from Studies 3069b and 3072b. The sponsor removed one patient from Study 3069b because the data appeared to be unreliable. The sponsor removed 7 patients from the analysis (6 on BNS, 1 on CT) in Study 3072b because they either:

- had been taking budesonide/Pulmicort Turbuhaler/Rhinocort for long periods of time at high doses before the beginning of open-label, or
- had great "variations in height data which were judged to be unreliable" (page 64, Vol 1).

No additional information was provided to describe these seven patients.

Reviewer Comment

This reviewer concurred with the sponsor that Patient #02-0234 from Study 3069b had measurements that appeared to be unreliable based on the previous six, (see graph for Patient #02-0234 in the Appendix page 22 and statistical review May 6, 1998, for further discussion). However, the reviewer's analysis included the reliable portion of this patient's data.

The sponsor did not identify which seven patients in Study 3072b were removed from the analysis nor how many were removed for each reason. The reviewer's analyses included all patients from Study 3072b.

3.3.2 Reviewer's Analyses

The company presented results of completers analyses that used growth velocity slopes standardized for the standard median height of each patient and change from baseline analyses adjusting for center and baseline height. This reviewer performed additional analyses on the data to determine the sensitivity of the results to the statistical methodology selected and the patients selected.

This review includes the analysis 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 slopes are estimates of growth velocity in centimeters per year. The mean slopes were compared across treatment groups using a linear regression adjusting for age. In summary, the results presented below show that the growth rates were different between the two treatment groups in Study 3069b (CT superior), and Studies 3072b and 3100b (BNS superior).

The company's analyses excluded patients who dropped out before 48 weeks. There were large differential dropout rates in Studies 3069b and 3100b. For the most part, both dropouts and completers appear to have grown linearly over time, (see individual patient data graphs in the Appendix pages 21-40). This argues for inclusion of subjects with at least 3 datapoints in an analysis of slopes. This reviewer performed both "completers" and "intent-to-treat" analyses on the

data. The completers dataset included patients who had who had at least 3 measurements and completed at least 300 days (10 months) of the study. The intent-to-treat dataset included patients who had at least 3 measurements and completed at least 60 days.[2]

\ linear regression was performed on the slopes, including baseline age and treatment group as covariates. Baseline age and baseline height were highly correlated (values ranged from 0.80-0.95), thus only one of the variables could be included in the models. Age was chosen because it explained more of the variability in growth velocity. In Studies 3069b and 3100b, age was included in the model as a function 1/age to account for the curvi-linear relationship between age and growth velocity (among patients between the ages of 9 months and 9 years), as depicted in the growth curve in the Appendix, page 13.

Table 6: Reviewer's Growth Velocity Analyses*

		3069b		3072b		3100b	
		CT	BNS	CT	BNS	CT	BNS
		N = 59	N =156	N = 26	N = 55	N = 74	N = 177
Compl	Mean Growth Velocity (cm/yr)	7.2	6.5	4.8	5.6	6.4	7.1
	Standard deviation	2.3	1.8	2.1	2.0	2.4	2.3
	Estimate of Trt Diff	**0.70**		**-0.94**		**-0.53**	
	95% CI	(0.22,1.2)		(-1.9,0.02)		(-1.0, -0.06)	
	p-value	0.0043		0.0552		0.0280	
	R2 / Adj R2	0.36/0.35		0.06/0.04		0.46/0.45	
		N = 74	N = 167	N = 26	N = 59	N = 87	N = 191
ITT	Mean Growth Velocity (cm/yr)	7.2	6.6	4.8	5.7	6.4	7.0
	Standard deviation	2.7	2.4	2.1	1.9	2.6	2.2
	Estimate of Trt Diff	**0.66**		**-0.97**		**-0.55**	
	95% CI	(0.07,1.2)		(-1.9,-0.03)		(-1.0,-0.09)	
	p-value	0.0272		0.0430		0.0184	
	R2 / Adj R2	0.28/0.28		0.06/0.04		0.43/0.42	

* Means are unadjusted. The estimate is the coefficient of the treatment variable in a linear regression on slopes with age and treatment group as explanatory variables. A total of ten unreliable observations were deleted from the three studies, (see Appendix page 14). The slope of Patient #27-0543 in Study 3069b was estimated to be -1.6 cm/yr. This patient was included in the analysis and the slope was changed to equal zero.

Age

An age-by-treatment interaction term was included in the models and not found to be statistically significant in any of the studies. Growth velocity means are presented in Table 7 by age group. The patients under 4 years were growing about 2-3 cm/yr faster than the older children on average. The treatment difference (favoring CT) in Study 3069b appeared to be greater in magnitude among the younger patients. Some of this difference may be due to the difference in ages. The treatment difference seen in Study 3100b above (favoring BNS) was not evident in the younger children, perhaps due to the age difference. The BNS patients <4 years old were, on average, 3 months older than the CT patients.

Table 7: Mean Growth Velocity (GV) by Age Group

	3069b		3072b		3100b	
	CT	BNS	CT	BNS	CT	BNS
<4 years	n = 17	n = 48			n = 23	n = 69
Mean GV (cm/yr)	9.6	7.7	(none)		8.6	8.3
Mean age (months)	27.9	30.8			28.2	31.5
≥ 4 years	n = 41	n = 104	n = 26	n = 52	n = 50	n = 104
Mean GV (cm/yr)	6.2	5.9	4.8	5.6	5.4	6.3
Mean age (months)	73.7	72.8	87.1	82.4	78.5	71.0

[2] One patient in Study 3069b (Pt #11-0172) had three visits and discontinued the study after 29 days. Two patients in Study 3100b (Pt#17-0240 and 25-0256) had three visits and discontinued the study after 58 and 49 days, respectively.

Gender

Girls on average grew faster than boys in Study 3069b; whereas in Studies 3072b and 3100b, the two groups grew about the same with boys' growth velocity slightly greater than girls. The boys in Study 3100b were slightly younger than the girls, possibly accounting for this difference.

Table 8: Mean Growth Velocity (GV) by Gender

	3069b	3072b	3100b
Males	n = 162	n = 51	n = 174
Mean GV (cm/yr)	6.6	5.6	7.0
Mean Age (months)	59.1	83.9	55.5
Females	n = 79	n = 34	n = 104
Mean GV (cm/yr)	7.2	5.2	6.7
Mean Age (months)	60.5	82.4	61.3

A gender-by-treatment interaction was included in the models and not found to be statistically significant in any of the studies. The means in each treatment group by gender are presented in Table 9, below. The differences seen in Study 3069b (favoring CT) were evident in both boys and girls. Similarly, the BNS advantage in growth velocity in Study 3072b was evident in both boys and girls. In Study 3100b, the difference (favoring BNS) was greater in magnitude in boys (0.8 cm/yr) than in girls (0.3 cm/yr).

Table 9: Mean Growth Velocity (GV) by Gender By Treatment Group

	3069b		3072b		3100b	
	CT	BNS	CT	BNS	CT	BNS
Males	n = 49	n = 113	n = 14	n = 37	n = 58	n = 116
Mean GV (cm/yr)	7.0	6.5	5.1	5.8	6.4	7.2
Mean age (months)	59.4	59.0	84.9	83.5	58.4	54.0
Females	n = 25	n = 54	n = 12	n = 22	n = 29	n = 75
Mean GV (cm/yr)	7.7	7.0	4.5	5.5	6.5	6.8
Mean age (months)	63.4	59.1	89.8	78.4	65.9	59.5

Reviewer Comment

The reviewer results for these studies are similar to those reported by the sponsor.

Table 10: Sponsor's and Reviewer's Estimates of Growth Velocity Treatment Differences (cm/yr)

	3069b	*3072b*	*3100b*
Sponsor's Analysis	*0.84*	*-0.71*	*-0.75*
Reviewer's Completers Analysis	*0.70*	*-0.94*	*-0.53*
Reviewer's ITT Analysis	*0.66*	*-0.97*	*-0.55*

The difference in the magnitude of the estimates is indicative of the sensitivity of the results to the method of analysis and selection of patients. Both approaches are post-hoc and assume that the potential biases previously described did not affect the estimates. It is difficult to determine which estimates (sponsor's or reviewer's) are closest to the true difference in treatment effects.

Overall, the sponsor's and reviewer's results show that in Study 3069b, there was a statistically significant treatment effect on growth velocity (favoring CT). The difference in Study 3072b (favoring BNS) was also statistically significant, however, the model only explained about 4-6% of the variability in growth velocity. The small difference in Study 3100b (favoring BNS) was more evident in the older children (≥ 4 years) and in the boys.

In addition to the potential bias and analytic problems described above, other factors affecting the results include differences in dropout rates and prednisone use. These issues are explored in the Appendix Sections 5.6 and 5.7.

4 Conclusions

The sponsor would like to include [redacted] in the labeling for BNS. The wording of the proposed label does not accurately reflect the differences in control groups in the three studies. [redacted] as stated in the proposed label, would suggest to the reader that t[redacted] However, the studies were markedly different in several ways:

- Different control groups (inhaled steroids vs. non-steroidal);
- Different asthma severity populations; and
- Different age distributions (2 studies included patients as young as 9 months).

Even if the label described these study differences [redacted] is not appropriate due to potential bias introduced by several factors:

- Patient self-selection (based on patient discontinuations immediately after randomization);
- Studies 3072b and 3100b not well-controlled: dose adjustment strategies of the assigned inhaled corticosteroid were different between BNS and control groups;
- Patient dropouts different across treatment and age groups;
- Extensive oral prednisone use;
- *Post-hoc* selection of data suitable for analysis (exclusion of specific patients due to unreliable measurements, inclusion of patients who completed specific length of time of study); and
- *Post-hoc* description of results (model-based mean change from baseline).

All of these factors undermine the quality of the data and the reliability of the estimates. This review maintains that [redacted] implies an acceptance by the Agency of the studies as "adequate and well-controlled", and of the estimates as accurate. Therefore, [redacted] should not be included in the label.

Additional Comments

In all three studies some of the patients on the budesonide treated arm and some of the patients on the inhaled corticosteroid control arms grew faster than expected and their growth appears to have been unaffected by inhaled corticosteroids, whereas others are growing slowly and may have been severely affected (see scatterplots on page 11). The individual variation in sensitivity to potential growth effects illustrates the need for prospectively designed studies with well-defined control groups and analyses that more fully investigate the individual response to corticosteroids. Mean differences in growth velocity from a post-hoc analysis of a study without a well-defined control group do not adequately address the needs of health care providers to individualize the treatment of asthma in their patients.

/S/

Barbara Elashoff
Mathematical Statistician

concur: Steve Wilson /S/ 2/4/99

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

5 Appendix

5.1 Scatter plots of Age and Growth Velocity

Figure A1

Study 3069b

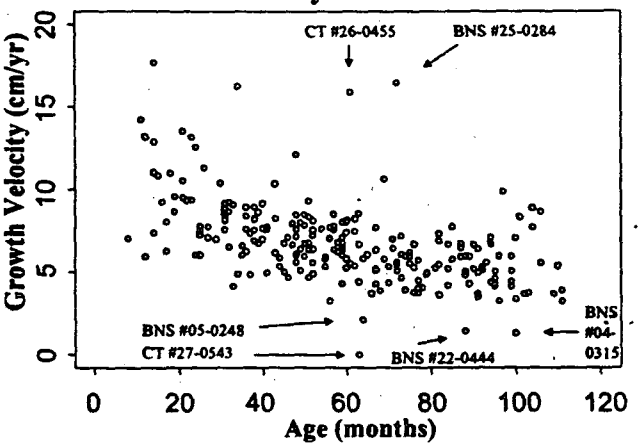


Figure A2

Study 3072b

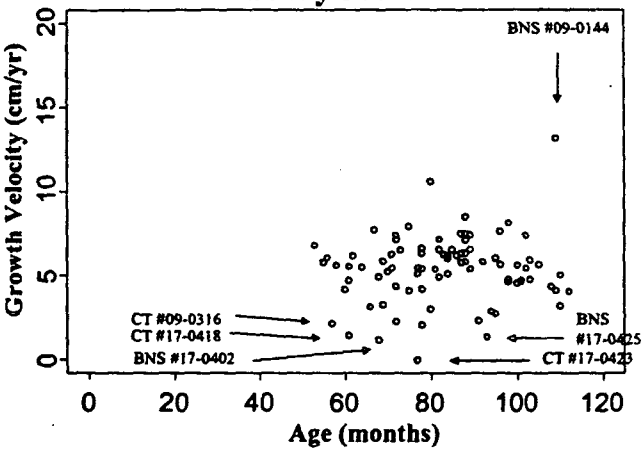
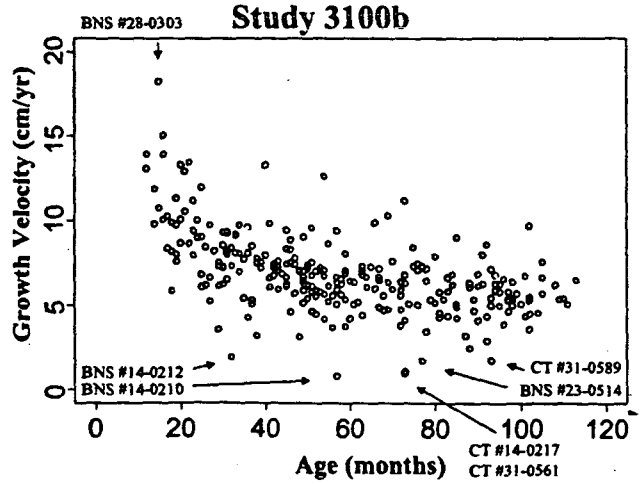


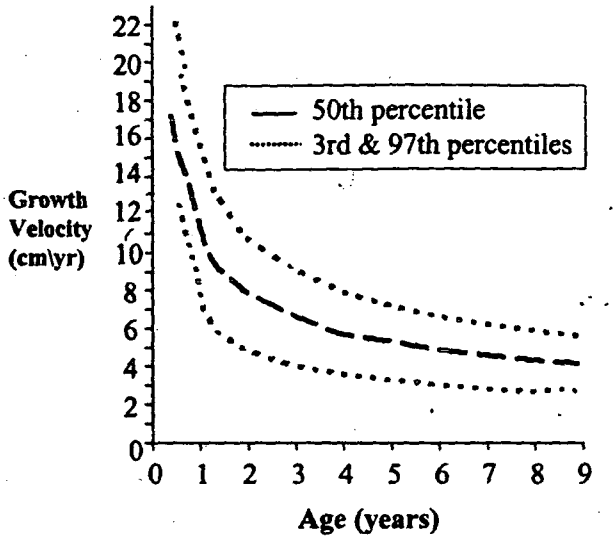
Figure A3

Study 3100b



5.2 *Growth Velocity Curve*

Figure A4



5.3 *Sponsor's Z-score*

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] or the formula of this standard deviation.[3]) 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.

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

5.4 Reviewer's Dataset Deletions

A number of observations were deleted from the dataset due to the unlikely values (see Table A1 below). These observations were unlikely relative to the observations around them. Individual patient graphs are on pages 21-40. The unlikely values can be seen graphically in the context of the values around them in these graphs. All observations from patients who were in the study less than 60 days were also deleted (see Table A2 below).

Table A1: Observations That Were Deleted From Dataset (likely to be errors)

Study	Patient	Visit(s)	Treatment
3069b	02-0234	7, 8	BNS
	03-0389	3	BNS
	05-0250	1	BNS
	11-0167	4,5	BNS
	18-0331	8	CT
3072b	01-0312	1	BNS
	17-0420	1	BNS
3100b	23-0512	7	CT

Table A2: Patients with <60 days on study deleted from dataset

Study	Patient	# of days in study	Slope	Treatment
3069b	11-0172	47	2.9	BNS
3100b	17-0240	58	2.2	BNS
	25-0256	49	0.0	BNS

5.5 Asthma Symptom Scores

Efficacy variables, such as daytime and nighttime asthma symptoms, were evaluated in the studies. The studies were not powered to detect differences in the efficacy variables, however in evaluating the safety effects of budesonide as compared to the control groups, it is useful to look at the potential numeric differences in these efficacy endpoints. The changes from baseline were calculated by subtracting the last observation for asthma symptoms recorded from the average of the last 14 days of the double-blind phase. (If the patients had already completed the double-blind phase and were called back to enter the open-label phase, the sponsor used the data from Visit 6A, see footnote #1, page 2). There were small differences (0.01 - 0.04) in change in daytime and nighttime symptoms (on a scale of 0-3) favoring the budesonide group in Studies 3069b and 3100b. For comparison purposes, in the double-blind phase of the studies, the differences with placebo were statistically significant and ranged from 0.26 to 0.44 units.

Table A3: Efficacy Results

	3069b		3072b		3100b	
	CT	BNS	CT	BNS	CT	BNS
Change in Nighttime Asthma Sx	-0.05	-0.09	-0.04	-0.03	-0.08	-0.10
Change in Daytime Asthma Sx	-0.09	-0.10	-0.02	-0.02	-0.10	-0.09

See Dr. Chu's review for a more extensive summary of the efficacy results.

Reviewer Comment

The baseline data used in these analyses was different for the patients who had a time-lapse between phases and the patients who entered the open-label phase immediately after the double-blind phase. Further, the baseline data was different for the patients with no-time lapse who were previously on BNS from those previously on placebo.

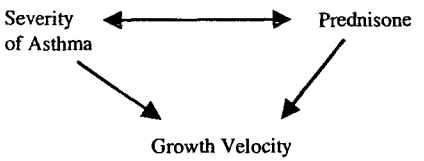
Of the 60% of patients who entered the open-label phase and who had been randomized to BNS in the double-blind phase, the baseline data are not useful for determining the efficacy of treatment in the open-label phase. Therefore, the differences in average changes in the efficacy parameters are not useful for determining the relative efficacies of the treatments in these studies.

5.6 Prednisone Use

Intermittent courses of oral prednisone were allowed for the control of asthma exacerbations, as judged necessary by the investigator. Prednisone has been shown to cause growth delay. The relationship between prednisone use, severity of asthma and growth velocity is complex. Since healthier patients may grow faster, it could be postulated that in comparison to the patients who did not use prednisone, the patients who did use it would either:

- grow slower because the patients who need to use prednisone probably have poorly controlled asthma; or
- grow faster because the asthma of the patients who use prednisone is more controlled.

Figure A5



Dropout rates and age may be related to these factors as well. For this reason, the use of prednisone in the studies was explored. Recall that the prednisone use was different between treatment groups in all three studies. A lower percentage of BNS patients used prednisone (at least once) in each of the three studies.

Table A4: Prednisone Use
(using reviewer's ITT dataset)
(%) of patients who used prednisone at least once*

	Study 3069b	Study 3072b	Study 3100b
CT	45/74 (61)	18/26 (69)	55/74 (63)
BNS	82/167 (49)	34/55 (58)	104/177 (54)

*Note that in calculating the percent of patients who used prednisone at least once, the sponsor included all the patients randomized (about 30% of whom they did not include in the calculations of their estimates of mean growth velocity), therefore the sponsor reported percentages that were different from these. The sponsor's percentages were more comparable across treatment groups.

The prednisone users appeared to be similar in terms of dropout rate and age (see Table A5 below). The two exceptions were in the Study 3069b BNS groups, the prednisone users were younger, on average than the non-users. The opposite was true in Study 3100. The growth velocity difference in Study 3069b (favoring CT) was present among the prednisone users only. Again, the opposite was true in Study 3100b.

Table A5: Descriptive Statistics of Prednisone Users and Non-users

	3069b		3072b		3100b	
	CT N= 74	BNS N= 167	CT N = 26	BNS N = 55	CT N = 74	BNS N = 177
Prednisone Users						
# (%) Dropouts	9/45 (20)	4/81 (5)	0/18 (35)	2/34 (6)	9/55 (16)	7/103 (7)
Average Age (months)	60	52	87	80	56	56
Average GV (cm/yr)	7.6	6.8	4.9	5.7	6.7	7.0
Prednisone Non-Users						
# (%) Dropouts	6/29 (21)	7/86 (8)	0/8 (0)	2/25 (8)	4/32 (13)	7/88 (8)
Average Age (months)	62	66	88	83	69	57
Average GV (cm/yr)	6.7	6.5	4.7	5.6	6.0	7.1

Of the patients who used prednisone, there were differences in amount of use between the studies.

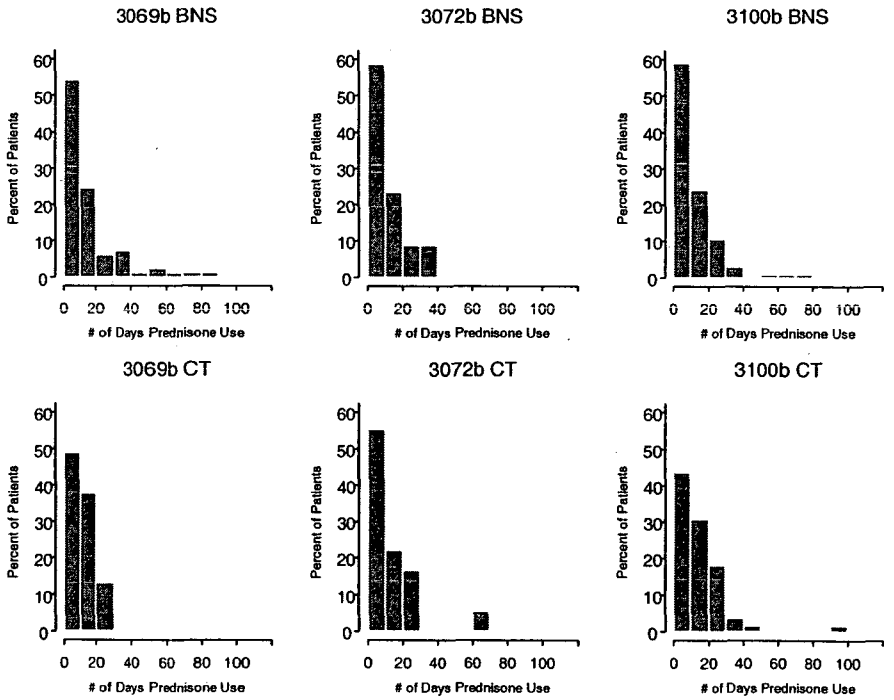
Table A6: Prednisone Use
(includes patients in reviewer's ITT dataset who used Prednisone at least once)

	3069b		3072b		3100b	
	CT	BNS	CT	BNS	CT	BNS
	n=45	n=82	n=18	n=34	n=55	n=104
Total pred dose (mg)						
Mean	286	338	591	407	350	343
Median	220	180	325	286	220	259
Total # days of OC						
Mean	12	16	15	12	15	13
Median	11.0	9.0	9.0	9.5	13.0	8.0
# (%) used ≥30 days	0 (0)	12* (15)	2 (11)	3 (9)	5 (9)	9 (7)
Max # days used	28	87	67	35	100	80
# (%) patients <4 years	14 (31)	35 (43)	0	0	24 (44)	41 (39)

*The mean growth velocity of the 12 BNS patients who used prednisone ≥30 days was 7.1 cm/yr. One of the 12 patients was a 15 month old (Patient #04-0587) whose estimated growth velocity was 11 cm/yr.

Prednisone use was highly skewed especially in the Study 3069b BNS group (see graphs below). In Study 3069b, the mean total prednisone dose, the mean total number of days, and the percent of prednisone users who were under four years was greater among the BNS patients. Further, 15 percent of the BNS prednisone users used it for more than 30 days compared to zero percent of the CT users. In general, the use was similar in Studies 3072b and 3100b with slightly greater use among the CT patients. Patient #26-0267 in Study 3100b used prednisone for 100 days. The estimate of the treatment effect was calculated with and without this patient and found to be identical (without patient #26-0267: -38 cm/yr). In Study 3069b, the mean growth velocity of the 12 BNS patients who used prednisone ≥30 days was 7.1 cm/yr, greater than that of the prednisone non-users. One of the 12 patients was a 15 month old (Patient #04-0587) whose estimated growth velocity was 11 cm/yr.

Figure A6: Histograms of Number of Days of Prednisone Use in Patients Who Used Prednisone At Least Once



Reviewer Comment

Note that the patients in Study 3069b who took prednisone grew faster, on average, than those that did not, especially among the CT patients. The average age of the CT patients was only slightly younger in the prednisone user group

therefore the difference did not appear to be due to differences in age. Perhaps the well-controlled asthma among the patients who took prednisone in the CT group led to an increased growth velocity.

In Study 3069b, the difference in growth velocities (CT superior) was evident among the prednisone users only (Prednisone Users: 1.2 cm/yr difference in means, Non-users 0.02 cm/yr). The opposite was true in Study 3100b (BNS superior, Prednisone Users: 0.3 cm/yr difference in means; Non-users: 1.1 cm/yr). The differences were about the same in the Study 3072b users. The different results in the three studies make it difficult to draw conclusions about the bias that may have been introduced by prednisone that would explain the results from all three studies.

5.7 Dropouts

With the exception of Study 3072b, the patients in the CT group dropped out more often than those in the budesonide group.

At ten months the dropout rates were different between treatment groups in Studies 3069b and 3100b.

Table A7: Number and Percent of Patient Discontinuation*

	Study 3069b	Study 3072b	Study 3100b
CT	31/90 (34)	4/30 (13)	29/103 (28)
BNS	24/182 (13)	7/61 (12)	26/204 (13)

* Discontinuation is defined here as: completed less than 10 months of the study.

Of the patients who had at least three datapoints and 60 days on-study (reviewer's ITT dataset), the percentages of dropout were smaller but the relative differences in dropout were similar. The one exception was Study 3072b which had a greater percentage of dropouts in the BNS group in this subset of patients.

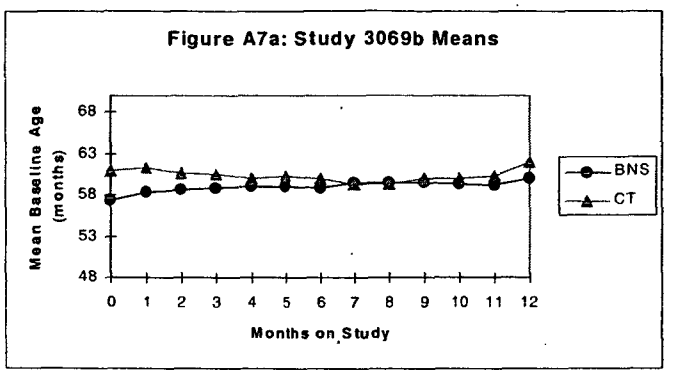
Table A8: Number and Percent of Patient Discontinuation (using patients in the reviewer's ITT dataset)

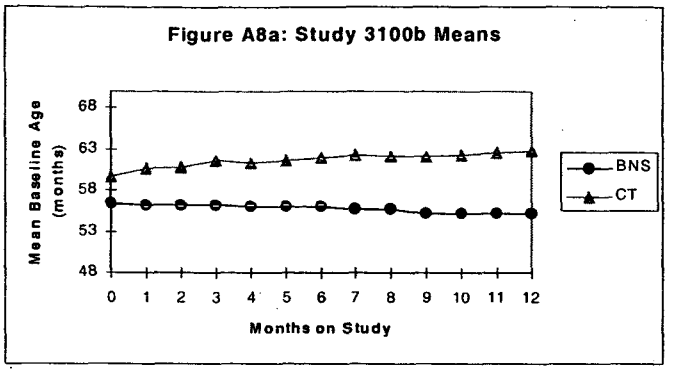
	Study 3069b	Study 3072b	Study 3100b
CT	15/74 (20.3)	0/26 (0)	13/87 (14.9)
BNS	12/168 (7.1)	4/59 (6.8)	16/193 (8.3)

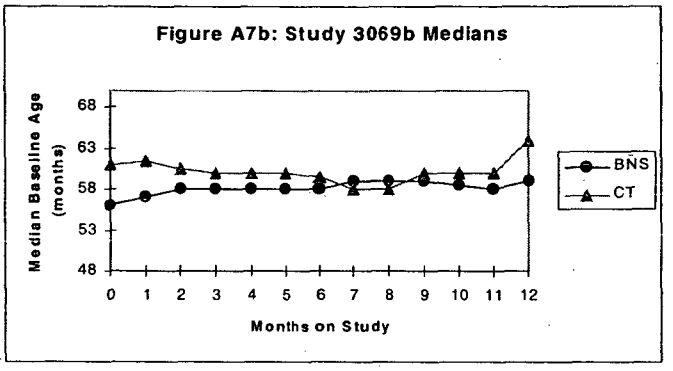
Reviewer Comment

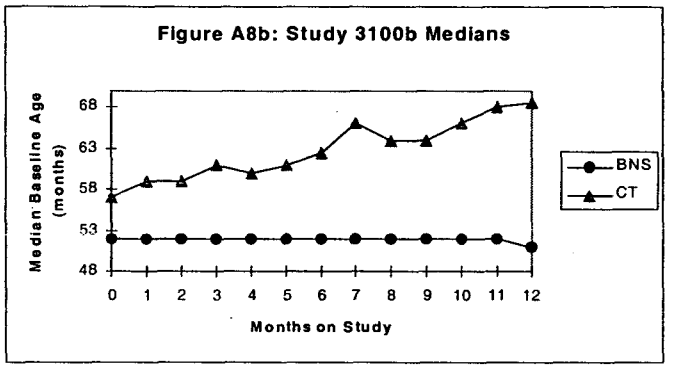
The direction and magnitude of effect the differential dropout rates in Studies 3069b and 3100b had on the study results is difficult to determine. Both the analyses with and without the dropouts are affected by this problem because excluding patients who drop out due to an event related to the outcome variable (such as disease severity) biases the results; and including the patients who do not have at least 10 months of data biases the results because the potential effect of the drug on growth may be cumulative over time.

Differential dropouts in age groups between treatment groups in Studies 3069b and 3100b (the studies with younger children) further complicate the issue due to the wide range of growth velocity between children ages 0-1, 2-3 and 4-9 years. Therefore, mean and median (baseline) ages of the cohort of patients remaining in Studies 3069b and 3100b at each month were examined (see Figures A7-A8 below). BNS patients in Study 3100b were, on average, younger, and the pattern of median age in the study over time was different between the two treatment groups. The younger patients dropped out at a greater rate on the CT arm than did the BNS patients.









The growth velocity curve for children is very steep from 0-1 years, less steep from 2-3 years and flatter still from 4-9 years (see Figure A4 in Appendix Section 5.2). Since differential dropouts among different age groups of patients could severely affect the results of the study, percentages of dropouts between treatment groups in all age groups were calculated (see Table A9 below). In Study 3069b it appeared that a higher percentage of children under 2 years in the BNS group (39%) dropped out than in the CT group (20%). The opposite was true in Study 3100b (BNS: 5%; CT: 50%). However in Study 3100b, most of the young discontinued patients dropped out before the second visit. Therefore, they had no change from baseline height data. These patients were not included in either the sponsor's analyses or the reviewer's analyses.

Table A9: N, Mean & Median Age of Dropouts By Age Group and By Time of Dropout;

		Study 3069b								Study 3100b							
		CT Total N Randomized = 90				BNS Total N Randomized = 182				CT Total N Randomized = 103				BNS Total N Randomized = 204			
				Age				Age				Age				Age	
		N Rand	N (%)	Mean	Med.	N Rand	N (%)	Mean	Med.	N Rand	N (%)	Mean	Med.	N Rand	N (%)	Mean	Med.
All Dropouts	< 24 months	10	2 (20)	16	16	18	7 (39)	14	14	16	8 (50)	18	19	19	1 (5)	12	12
	24 mos - 3 yrs	18	8 (44)	37	37	45	6 (13)	35	33	24	8 (33)	35	37	61	8 (13)	41	42
	>=4 years	61	20 (33)	75	70	116	10 (9)	82	86	63	13 (21)	78	74	123	17 (14)	82	84
Dropped out before day 60	< 24 months		2	16	16		3	11	11		6	20	21		1	12	12
	24 mos - 3 yrs		2	33	33		3	37	42		3	28	25		4	41	43
	>=4 years		9	75	73		4	82	86		5	87	87		7	85	84
Dropouts Between 60 and 300 days	< 24 months		0				4	16	16		2	15	15		0		
	24 mos - 3 yrs		6	38	38		3	32	31		5	39	38		4	40	41
	>=4 years		11	76	69		6	81	86		8	72	70		10	80	81

Of the patients who were included in the analyses, the percent of patients under 2 years was balanced across treatments in Study 3100b, but not in Study 3069b (Study 3060b Completers: CT 14%, BNS 7%; Study 3100b Completers: CT 11%, BNS 10%, see Table A10 below). Because the sample sizes were different, the 11 infants in the BNS group at 10 months contributed less to the overall mean growth velocity estimate of BNS than the 8 infants in the CT group did to the growth velocity estimate of CT. In Study 3100b, the two groups of infants contributed similarly to the estimates of growth velocity.

Table A10: N, Mean & Median Age of Patients In Reviewer's ITT and Completers Datasets

		3069b						3100b					
		CT			BNS			CT			BNS		
			Age			Age			Age			Age	
		N (%)	Mean	Med.	N (%)	Mean	Med.	N (%)	Mean	Med.	N (%)	Mean	Med.
ITT	< 24 months	8 **(11)**	**19**	20	13 **(8)**	**16**	15	10 **(11)**	**18**	19	18 **(9)**	**18**	19
	24 mos - 3 yrs	15 **(20)**	**37**	36	42 **(25)**	**35**	36	20 **(23)**	**35**	34	57 **(30)**	**36**	36
	>=4 years	51 **(69)**	**74**	67	112 **(67)**	**73**	73	57 **(66)**	**78**	78	116 **(61)**	**72**	67
	Overall	74	**61**	61	167	**59**	58	87	**60**	59	191	**56**	52
Comp	< 24 months	8 **(14)**	**19**	20	11 **(7)**	**16**	17	8 **(11)**	**19**	19	18 **(10)**	**18**	19
	24 mos - 3 yrs	10 **(17)**	**37**	37	39 **(25)**	**35**	36	16 **(22)**	**33**	31	53 **(30)**	**36**	36
	>=4 years	41 **(69)**	**74**	67	106 **(68)**	**73**	73	50 **(68)**	**79**	80	106 **(60)**	**71**	67
	Overall	59	60	60	156	59	59	74	62	66	177	55	52

* Note that the means in this table are rounded off to the nearest integer, and the completers dataset includes patients who remained in the study at least 10 months. Therefore, the overall averages and medians in this table correspond to the values in Figures 3 and 4 at 10 months, rounded off to the nearest integer.

Figure A7b above demonstrates that the children in Study 3100b on the CT arm were older than the children on the BNS arm. This difference is evident only among the children 4 years and older (see Table 13 above). The percentages of children in each age group are evenly distributed across treatments and the mean and median ages of the children in the "<24 months" and "2-3 yrs" age groups are similar as well. The only age group that is different is the "4 yrs and older" (Median age CT: 80 months or 6.7 years; BNS: 67 months or 5.6 yrs). Since the greatest representation is of the oldest age group, this difference was clearly evident in the graphs of the overall means and medians.

Reviewer Comment

The high rate of initial dropout among the younger children in both studies is indicative of the difficulties of performing these long-term growth studies in young children with asthma. The open-label nature of these studies coupled with the high incidence of dropout before the second visit decrease the confidence in the estimates of treatment difference because the fundamental part of a clinical trial, randomization, was violated by self-selection into the study.

The greater percent of children under 24 months on the CT arm in Study 3069b may bias the results in favor of CT. However, the average age of the children under 24 months on the CT arm is actually 3 months greater than that of the patients on the BNS arm under 24 months. The wide range of normal growth velocity of children under 24 months (50th percentile: 8-17 cm/yr, see Figure A3 in Appendix Section 5.2) means that an average difference of three months could translate into an average growth velocity difference of at least 1 cm. Therefore, it is difficult to determine the direction of the overall bias introduced by the difference in percent of children under 24 months and the difference of mean age of these patients.

Among the older cohort of patients ≥4 years) in Study 3100b the BNS children were, on average, 1 year younger. The growth velocity curve of children is not as steep as it is among children <2 years. Therefore, the fact that the children are younger on the BNS arm in Study 3100b (among the cohort of older children) may not affect the growth velocity differences as much as the differences in age did in children <24 months in Study 3069b.

5.8 Individual Patient Graphs

The change from baseline in height (cm) is graphed for each patient on the following pages. The patients are sorted by study, treatment and patient identification number, in that order. Printed above each graph are the patient's identification number, age (in months), and gender ("M" or "F"). If the patient used oral corticosteroids at all during the study, the measurements are connected by a dashed line and the total amount of oral corticosteroid use is printed in milligrams and number of days on the graph.

19 Page(s) Withheld

TPOUT

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date:
MAY 6 1998

NDA#:	**20-929**
Applicant:	**Astra USA, Inc.**
Name of Drug:	**Pulmicort Respules (budesonide nebulizing suspension)**
Indication:	**Asthma**
Documents Reviewed:	**7-18-97, 7-25-97 IND 044535 (electronic data and study reports submitted to IND 44, 535)** **11/20/97 NDA 20-929** **1-7-98; 3-6-98** **fax: 3/27/98**
Statistical Reviewer:	**Barbara Elashoff, M.S.**
Medical Input:	**Shan Chu, M.D.**

Summary

- The applicant has submitted three placebo-controlled 12-week studies (Study 3072, n=178; Study 3069, n=359; Study 3100, n=481) to support the claim that budesonide nebulizing suspension is safe and effective in reducing the symptoms of asthma in children ages [redacted] to eight years. [redacted] A four-point rating scale was used to assess nighttime and daytime symptoms, separately. In these studies reductions in nighttime symptoms ranged from -.08 to -.16 units for placebo and -.36 to -.49 units for active drug. The reduction in daytime symptoms ranged from -.11 to -.26 units for placebo and -.37 to -.57 units for active drug. Studies 3069 and 3100 continued as open-label safety studies for an additional year. The sponsor submitted the results of the open-label part of Study 3069. (Study 3100 was not yet complete at the time the NDA was submitted.)

- The studies were designed to demonstrate that BNS is efficacious for both nighttime and daytime symptoms. Therefore, statistical significance on both nighttime *and* daytime symptoms was necessary for the results of a treatment group to be declared statistically significantly different from placebo.

- Study 3069 included three QD doses, while Study 3072 included three BID doses and Study 3100 included both dosing regimens (two QD and two BID). The results of the studies should be examined cautiously because there is an increased likelihood of statistical significance when making multiple comparisons between each of the dose groups and placebo.

- Efficacy of the .25 mg BID dose group was clearly established in both studies in which it was included (3072 and 3100).

- The results for the .5 mg BID group (for both daytime and nighttime symptoms) in Study 3100, and for daytime symptoms in Study 3072 strongly supported efficacy. The .5 mg BID dose group did not achieve statistical significance for nighttime symptoms after adjusting for multiple comparisons (each dose with placebo). However, the treatment effects were almost identical to those of the other two groups which did achieve statistical significance. In addition, the .5 BID group performed better

than the .25 BID group in a number of secondary efficacy variables. Therefore, the results from Studies 3072 and 3100 support an efficacy claim for the .5 mg BID.

- The results of the 1.0 mg BID dose group were statistically significant for both nighttime and daytime symptoms in Study 3072, but these results were not replicated as the 1.0 mg dose group was not included in another study.

- The only once daily dose that relieved both daytime and nighttime symptoms (after adjustment for multiple comparisons) was .25 mg QD in Study 3069. However, this finding of statistical significance was not replicated in Study 3100.

- Overall, the results of the studies demonstrate efficacy of the BID dose groups. In addition, there was no apparent increase in efficacy in the primary variables with increasing dose above the .25 mg BID dose in any of the studies.

- Studies 3069 and 3100 included a total of 122 patients less than two years old (99 of these were on BNS). The treatment effects for the patients 2 years and younger were similar to those above two years for both daytime and nighttime symptoms in both studies, despite the fact that the symptoms were not self-reported.

- After patients completed the 12-weeks of double-blind treatment period in Study 3069, they had the option of continuing in the open-label phase (called Study 3069b), if they met entrance requirements. 89% of the patients continued. This study suggested that BNS affected growth velocity (at a rate of approximately .76-.85 cm/year), however, these findings should be regarded cautiously in the context of the problems with the study design which may have over- or under-estimated the treatment effect (i.e., unblinded treatments, self-selection into the study, previous use of study drug with no washout period, sensitivity of results to *post-hoc* selection of data and analysis, and differential prednisone use).

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1. Efficacy

1.1 Introduction

Table 1: Primary Efficacy Studies*

	Study Number		
	04-3069 (N=359)	04-3072 (N=178)	04-3100 (N=481)
Dates Conducted	8/94-12/95	5/94-11/96	5/95- 6/96
Dose Regimen (all QD doses dosed in the morning)	Placebo 0.25 mg QD 0.5 mg QD 1.0 mg QD	Placebo 0.25 mg BID 0.5 mg BID 1.0 mg BID	Placebo0.25 mg QD0.25 mg BID0.5 mg BID1.0 mg QD
Patient Population -Ages	6 months to 8 years	4-8 years	6 months to 8 years
-Severity of Asthma	Non-steroid dependent asthmatic patients	Inhaled steroid dependent asthmatic patients	mild to moderate asthmatic patients
Treatment Period	12 weeks	12 weeks	12 weeks
Number of Investigators/Sites	28 investigators at 26 sites	18 investigators at 17 sites	38 investigators at 38 sites
Primary Endpoints	Daytime & Nighttime Sx	Daytime & Nighttime Sx	Daytime & Nighttime Sx
Asthma Medications allowed prior to randomization	Bronchodilators, cromolyn sodium, nedocromil sodium	Inhaled steroids (required), bronchodilators, cromolyn sodium, nedocromil sodium	Inhaled steroids (optional), bronchodilators, cromolyn sodium, nedocromil sodium

*All studies used the Pari LC-Jet Plus/Pari Master Nebulizer/Compressor System.

Baseline Run-In Period

All studies had a baseline run-in period of 2-3 weeks. The patients who had a score of 1,2 or 3 for daytime or nighttime asthma for at least 5 of the 7 last days of baseline were randomized. The averages of the symptom scores from the patients' last 7 days of baseline period were used as the baseline scores.

Entrance Requirements

The patients enrolled in Study 3072 were older (4-8 years) and had more severe asthma (required inhaled steroids) than those in the other studies. However, the baseline scores of daytime and nighttime asthma and PEF scores, were similar across the studies (see Appendix Tables 1-3).

Stratified Randomization

For Studies 3069 and 3100, the randomization was stratified, based upon the patients' ability to perform Pulmonary Function Tests (PFTs). The ability to perform was related to the patients' age. Most patients able to perform PFTs were between five to eight years, while most patients unable to perform PFTs were between 6 months and four years of age.

1.2 Efficacy Variables

1.2.1 Primary Efficacy Variables

The two co-primary endpoints in all three studies were the changes from the average of the last 7 days of the baseline period before randomization to the average of the double-blind phase (Weeks 0-12) for both daytime and nighttime asthma symptoms (scale 0-3). Daytime and nighttime assessments were reflective over the previous 12-hour period.

Reviewer Comment
The studies were designed to detect statistically significant differences between placebo and BNS for both nighttime and daytime symptoms, therefore no multiple comparisons adjustment was needed for making these two comparisons. (However, a multiple comparisons adjustment was needed to make the three - Studies 3069 & 3072- and four -Study 3100- comparisons between the various doses and placebo in each study. The Step-Down Procedure could not be used in Study 3100 because there were two dosing regimens that yielded the same total daily dose. The sponsor chose not to specify any multiple comparisons procedure before breaking the blind.)

Daily Diary Cards
Each patient or caregiver assessed the patient's symptoms and recorded the scores in daily diary cards.

Reviewer Comment
The patients who were old enough to assess their own symptoms and record the scores themselves presumably did so. In a telecon dated November 15, 1996, Astra stated that the person who filled out the diary card was not recorded on the case report form, therefore, they did not know if the recorder was the patient or the parent. In pediatric studies (ages 4 and above) the results of the patients' global assessments and the parent's global assessments are not always similar, indicating that the outcome variables in Studies 3069 and 3100 (with patients <4 years) may be related to who filled out the diary cards, a factor that cannot be modeled. In these studies, there are three types of patient diary assessments:

1. *those filled out by the patient;*
2. *those filled out by the parent, but the child is speaking and can communicate symptoms to the parent; and*
3. *those filled out by the parent, and the child is too young to communicate symptoms to the parent.*

Therefore, these results should be interpreted with caution.

1.2.2 Secondary Efficacy Variables

The sponsor pre-specified several secondary efficacy variables:

1. Number of days use of breakthrough medication;
2. The amount of breakthrough medication used;
3. Overall discontinuation rate;

4. Treatment failures (defined as 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)
5. Health status (Study 3069 only);
6. Health care utilization (Study 3069 only);
7. Indirect economic endpoints (Study 3069 only);[1]
8. PFT's (For Studies 3069 & 3100, the following variables were only assessed in the subpopulation of patients who were able to use peak flow meters correctly);
    a) morning PEF
    b) evening PEF;
    c) FEV_1;
    d) FVC with corresponding $FEF_{25-75\%}$ at the clinic setting

1.3 Statistical Analysis

The primary efficacy analysis was an analysis of variance (ANOVA) with the change from baseline as the dependent variable and center and treatment as factors. Baseline was not included in the model. Center was included in the model and represented more than one investigator at certain centers.

Reviewer Comment
There was more than one investigator at some centers and the factor "center" in the model represented each investigative site rather than each investigator. Therefore, center effect does not fully account for investigator-to-investigator differences in assessing and treating a patient (only variability associated with other effects, i.e., location and pollen levels).

In a telecon dated November 15, 1996, the FDA recommended that the sponsor use some type of multiple comparisons procedure because the sponsor was planning to look at the comparisons of each dose with placebo. FDA advised the company to rewrite the statistical analysis plan including this analysis (regarding the multiple comparisons problems) and resubmit it to the FDA. The company did not resubmit an analysis plan before the blind was broken, but did use the type of multiple comparisons procedure that FDA recommended in the telecon (the Dunnet-type adjustment).

The sponsor used
1) a Dunnett-type adjustment procedure for the analysis of the primary efficacy variables; and
2) the Step-Down Procedure by Dunnett and Tamhane to determine the minimal effective dose.

The Dunnett-type adjustment procedure adjusts the standard deviations of the means to account for the increase in the uncertainty of the results. However, it compares the means of the treatments across all centers; it does not adjust for center. When the means and confidence intervals of the differences between placebo and BNS groups are close together, center may have an impact on the relative magnitudes of the different dose results. (This phenomenon occurred in Study 3072, discussed in footnote #2 on page 11.)

The Step-Down procedure is only applicable in the two studies in which the total daily doses are different. (Study 3100 has two total daily doses that are equal.)

[1] The secondary endpoints, Health Status, Health Care Utilization and Indirect Economic Endpoints, are not discussed in this review.

1.4.1 Demographics

Gender

The basic demographic characteristics were similar for the four treatment groups in all three studies, with the exception of gender in Study 3072 (see Appendix Tables 4-6). In Study 3072, the majority of patients in the BNS groups were male (ranging from 61.8% - 71.4%) and the majority of patients in the placebo group were female (54.5%). The difference in proportions of males between the placebo group and a combination of all BNS groups was statistically significant (21.7%; p=.0125).

Reviewer Comment

Possible differences between treatment effects across gender are discussed with the results of the studies, see Section 1.4.9, page 15. The treatment effects appeared to be similar in males and females.

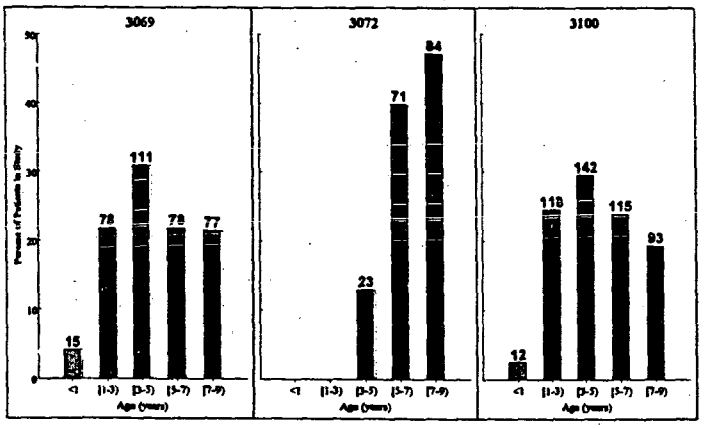
Age Distribution

The patients in Study 3072 were between the ages of 4 and 8 years old, whereas the patients in Studies 3069 and 3100 were as young as 6 months. There were 15 patients less than one year old on active treatment in Study 3069 and 12 in Study 3100. However, most patients were older than three years. Figure 1 is a bar chart of the percent of patients in each age group. The number of patients in each age group is printed above each bar. Means and standard deviations of age are presented in Appendix Tables 4-6.

Reviewer Comment

Possible differences between treatment effects across age subgroups are discussed with the results of the studies, see Section1.4.9, page 15. The treatment effects appeared to be similar in the patients under and over two years of age.

Figure 1



1.4.2 Baseline Scores

The baseline values of daytime and nighttime asthma scores and pulmonary function tests were similar across treatment groups, see Appendix Tables 1-3. The entrance requirements for Study 3072 included a requirement that the patients be on inhaled steroids prior to randomization, whereas this was optional in Study 3100, and not allowed in Study 3069. The baseline asthma symptoms in Study 3072 do not appear to be any higher, and the pulmonary function test results any lower, than those in the other two studies. (Perhaps due to the fact that the patients were using inhaled steroids.)

The baseline means of the patients less than 24 months in Studies 3069 and 3100 are similar to those of patients greater than 24 months, see Table 2 below.

Table 2: Baseline Asthma Symptoms By Age Group

			Daytime		Nighttime	
Study	Age Group	n	mean	std dev	mean	std dev
3069	≤ 24 months	52	1.27	.55	1.25	.64
	> 24 months	306	1.35	.53	1.19	.51
3100	≤ 24 months	70	1.37	.51	1.31	.64
	> 24 months	401	1.27	.50	1.20	.62

1.4.3 Dropouts

Table 3: Summary of Patient Discontinuations

		Placebo	0.25 QD	0.25 BID	0.5 QD	0.5 BID	1.0 QD	1.0 BID	Total
3069	total n	92	91		83		93		359
total discontinued	n	26	17		20		13		76
	(%)	(28%)	(19%)		(24%)		(14%)		(21%)
	p-value		0.1630		0.6070		0.0196		
discontinued due to worsening asthma	n	21	13		14		12		60
	(%)	(23%)	(14%)		(17%)		(13%)		
3072	total n	44		47		42		45	178
total discontinued	n	19		6		5		9	39
	(%)	(43%)		(13%)		(12%)		(20%)	(22%)
	p-value			0.0019		0.0016		0.0232	
discontinued due to worsening asthma	n	16		5		1		6	28
	(%)	(36%)		(11%)		(2%)		(13%)	
3100	total n	95	94	99		98	95		481
total discontinued	n	37	20	21		19	29		126
	(%)	(39%)	(21%)	(21%)		(19%)	(31%)		(26%)
	p-value		0.0110	0.0079		0.0041	0.2861		
discontinued due to worsening asthma	n	25	15	13		15	20		88
	(%)	(26%)	(16%)	(13%)		(15%)	(21%)		

P-values are from a two-sided Fisher's Exact test comparing each BNS dose to placebo.

- **Study 3069:** A total of 76 (21%) randomized patients were discontinued from the treatment phase of the study. Sixty of these 76 discontinuations (79%) dropped out due to worsening symptoms of asthma. The proportion of the patients in the placebo group that dropped out was greater than that of any of the treatment groups, as was the proportion of patients who dropped out due to worsening symptoms of asthma.

- **Study 3072:** A total of 39 (22%) randomized patients were discontinued from the treatment phase of the study. Twenty-eight of these 39 discontinuations (72%) dropped out due to worsening symptoms of asthma. A Fisher's Exact Test was used to analyze the differences in proportions of patients who dropped out between the treatment groups. The proportion of dropouts in the placebo group was statistically significantly greater than that of each of the treatment groups. In addition, the proportion of dropouts who dropped out due to worsening symptoms of asthma was statistically significantly greater than that of each of the treatment groups.

- **Study 3100:** A total of 126 (26%) patients were discontinued from the double-blind treatment phase of the study. Eighty-eight of these 126 discontinuations (70%) dropped out due to worsening symptoms of asthma. The proportion of the patients in the placebo group that dropped out was greater than that of any of the treatment groups, as was the proportion of placebo patients that dropped out due to worsening symptoms of asthma. The proportion of patients in the placebo group that dropped out was statistically significantly greater than that of the .25 QD and BID groups and the .5 BID group. The proportion of patients in the placebo group that dropped out due to worsening symptoms was statistically significantly greater than that of the .25 BID group.

Reviewer Comment

Of the three studies, Study 3072 (the study of steroid dependent asthmatics, 4-8 years of age) had the most pronounced difference in dropout rate due to worsening symptoms between the placebo group and the BNS groups. This large imbalance affected the results of the ITT analysis (using last observation carried forward for missing values) and the results of the per protocol analysis (using data from patients who completed the study). The placebo group had the highest rate of dropouts due to worsening symptoms. Therefore, the average placebo response in the per protocol population was greater than that in the ITT population, yielding smaller differences between BNS and placebo in the per protocol analysis. Conversely, this large imbalance yielded larger differences between BNS and placebo in the ITT analysis, because the high symptom scores of the patients who dropped out (due to worsening symptoms) were carried through to the end of the study.

Age Differential Dropout

The patients less than 2 years old in Studies 3069 and 3100 dropped out more often than did the older children, see Table 4 below. In Study 3069, by the tenth week, the dropout rate for the younger children and infants was almost twice that of the older children, (32% for the ≤24 months vs. 19% of the >24 months). In Study 3100, these percentages were 35% and 26% for the younger and older children, respectively. Further, the younger children in Study 3069 dropped out earlier than the older children: by the third week, 15% of the younger children had already dropped out whereas only 5% of the older children had left the study. The distributions of the dropout rate between age groups were similar across treatment groups in both studies. Therefore, these observed differences may have had little effect on estimates of the overall treatment effect. The possible difference in treatment effects of the subgroups is discussed in Section 1.4.9, page 15.

Table 4: Dropouts by Age Subgroup

		N (%) completed <10 weeks	Total n
Study 3069	≤ 24 months	17 (32%)	53
	> 24 months	57 (19%)	306
Study 3100	≤ 24 months	25 (35%)	71
	> 24 months	106 (26%)	410

1.4.4 Primary Efficacy Variable

Below is a summary table of the results of all the studies.

Table 5: Summary Table of Results of all 3 Studies

Sample Size

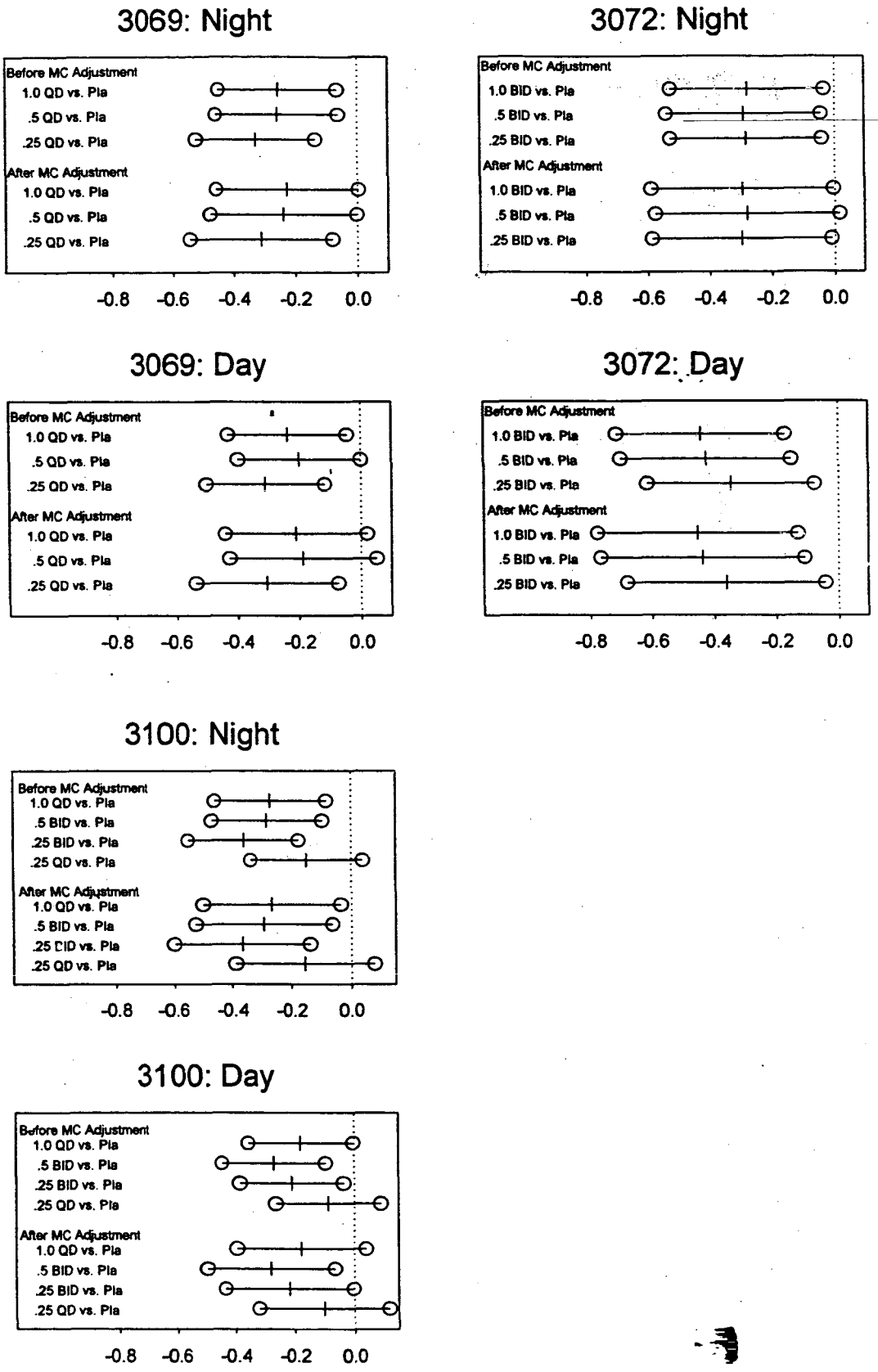
increasing dose. The mean changes from baseline for the .25 mg BID, .5 mg BID and 1.0 mg BID groups were: -0.45, -0.53, -0.55, respectively. The p-value for the linear contrast was not statistically significant (p=0.5334). Nighttime symptoms did not increase with increasing dose.

- **Study 3100:** Treatment groups with both BID and QD dosing were included in this study. The BID dose groups were more effective than the once daily dosing regimens, after adjusting for multiple comparisons. Only the results of the .25 mg BID and .5 mg BID groups were statistically significantly different than placebo for *both* daytime and nighttime symptoms. Dose Response: For nighttime symptoms, the treatment effect of .25 mg BID was numerically superior to that of the .5 mg BID dose group, whereas the opposite occurred for daytime symptoms. Therefore, efficacy did not increase with increasing dose.

Reviewer Comment

The results of the studies should be examined cautiously because of the increased likelihood of statistical significance when making multiple comparisons. After adjustment for multiple comparisons using the Dunnett-type adjustment, only the .25 BID dose is consistently statistically significant in more than one study. However, the results describing statistical significance should not be the only factor in determining efficacy. 95% confidence intervals of the differences in the means (before and after adjustment for multiple comparisons) are presented in Figure 2. The graphs depict the strength of the results of the studies (rather than just a significant/not significant result). Overall, results of the three studies support the conclusion that there was a statistically significant difference in reduction of nighttime and daytime symptoms between the twice daily dosing of BNS and placebo. There was no increase in effect with increasing dose. The efficacy of the once daily dosing of BNS was not demonstrated.

Figure 2: Treatment Effects Before & After Multiple Comparisons Adjustment



1.4.5 Secondary Efficacy Variables

There were a number of secondary efficacy variables in the three studies. In general the results were similar to the results of the primary efficacy variables: the BID dose groups consistently performed well compared to placebo across studies, whereas the results of the QD dose groups were not consistent across studies. Details are provided in the appendix Tables 7-11, pages 40-43.

1.4.6 Center Differences

It was difficult to compare the results across centers because there were four to five treatment groups in the studies. Combining the active treatment groups provided a way to identify differences of an overall "BNS" treatment effect across centers. None of the centers appeared to dominate the analysis, see Appendix Figures 1-6. With the exception of a large negative effect in Center #9 in Study 3100, there were no obvious differences between centers in any of the studies. The p-value of the center-by-treatment interaction in the analysis of nighttime symptoms in Study 3100 was 0.1004.[3]

Reviewer Comment

The marginally statistically significant center-by-treatment interaction in Study 3100 was probably due to Center #24, with nine patients. Twenty-two of the 33 centers favored the combined BNS treatment group, therefore, it is likely that the negative treatment effect from Center #24, one of the smallest centers, was an anomaly.

1.4.7 End of Dosing Interval

The treatment effect of BNS was assessed at the end-of-dosing interval for patients who could perform pulmonary function tests (PFTs) (see results in appendix page 41). For the patients who were too young to perform the tests, there was no end-of-dosing interval assessment recorded.

Reviewer Comment

The patient population for which there was end-of-dosing interval data was somewhat undefined because there was no strict age cutoff for the PFTs. Some patients between the ages of 4 and 5 were able to perform the tests, and some were not. Therefore, these test results are difficult to strictly apply to specific age groups.

1.4.8 Onset of Action and Sustained Effect

The sponsor would like to define onset of action as the first occurrence of a statistically significant difference between the treatment and placebo. Using this definition, the sponsor determined the onset of action to be between a few days to two weeks. The sponsor included graphs of the means of the data for the first 14 days and weekly data (2-week averages) using last observation carried forward to support this claim. The results were sporadic through the first two weeks, (see the medical officer's review for the sponsor's graphs of the first 14 days). After two weeks, the large differences between BNS groups and placebo appeared to be sustained through the remaining weeks of the studies, see Appendix Figures 7-10.

[3] Three centers in Study 3100 were excluded from the graphs because they did not have any patients in the placebo arm and there was no way to estimate a treatment difference. One center was excluded because it had only 1 patient on placebo and 1 on BNS. A variance around the treatment effect in this center could not be calculated.

Reviewer Comment

The two terms, "onset of action" and "sustained effect" are closely related and therefore are discussed together in this review. The sponsor would like to define onset of action as the first occurrence of a statistically significant difference between the treatment and placebo. An alternative definition of onset of action could be the time until the symptom scores reach a difference from placebo, the approximate magnitude of which is generally maintained throughout the trial. Sustained effect may be defined as the maintenance of treatment effect throughout the trial. It appears as though the onset of effect and the maintenance of that effect was different for different treatment groups and different symptoms.

The percentage of dropouts in the three studies was 21%, 22% and 26%, for Studies 3069, 3072 and 3100. The sponsor carried forward the last observations of the dropouts to impute missing values. The sponsor's graphs are of means calculated using the data carried forward. The numbers of actual patients remaining in the study, recording actual symptom scores, contributing to each mean decreases as the time variable on the x-axis increases. Further, after some patients have dropped out, as the time variable increases, the number of days since dropout increases making the last value of each dropout patient a poorer and poorer estimate of what the patient would have recorded had s/he stayed in the study. Meanwhile, as the time variable increases, the ratio of the number of such poor estimates used in calculating each mean increases relative to the number of real values.

This reviewer used "all available data" instead of imputing missing values with the last observation, see Appendix Figures 11-16. Two columns of graphs are presented per page. The graphs in the first column of each page are the "change from baseline" graphs. The graphs in the second column of each page are the means of the "observed values" at each visit. 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 simplicity. Graphs of the means of days 1-21 and of one week intervals are presented. These graphs should be used in addition to the sponsor's graphs to assess the onset of action and to determine if the treatment effect is sustained throughout the 12 weeks. The patients who remained in the trial generally had lower symptoms than of those who dropped out. The placebo patients had the highest rate of dropout (see Table 3, page 8), thus the placebo symptom score means, in the "all available data" graphs were closer to the BNS groups than they were in the sponsor's LOCF graphs.

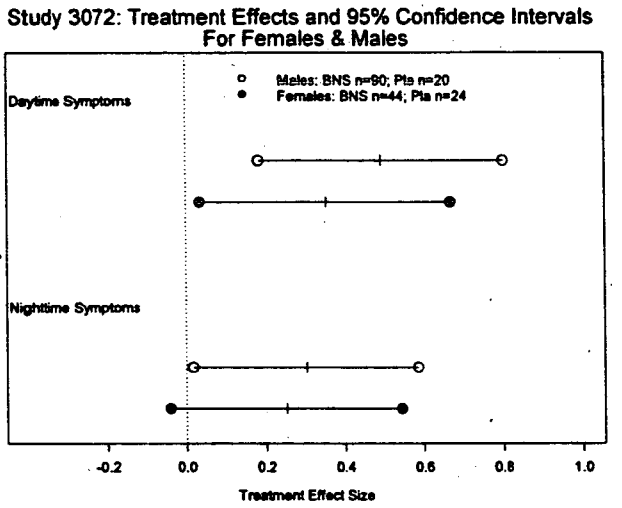
Overall, for the two symptom scores, the treatment effects of the different BNS groups appeared to start acting between days 7 and 21, depending on the symptom and the dose level. The treatment effect appeared to be sustained throughout the remaining weeks of the trials.

1.4.9 Subgroup Analyses

Gender

Recall that in Study 3072, the majority of patients in the BNS groups were male (ranging from 61.8% - 71.4%) and the majority of patients in the placebo group were female (54.5%). The difference in proportions of males between the placebo group and a combination of all BNS groups was statistically significant (21.7%; p=.0125). The treatment effects were assessed in the two different treatment groups using a model including a gender-by-treatment interaction term. The males had a slightly larger treatment effect for both daytime and nighttime symptoms, but the differences between males and females were small and not statistically significant, see Figure 3 below.

Figure 3



Age

BNS is the first glucocorticosteroid to be studied in patients less than two years old, therefore it is of interest to examine whether there is a different treatment effect among these patients than there is among the patients older than two years.

Figures 4 and 5 below are graphs of the treatment effects and 95% confidence intervals for the different age groups in Studies 3069 and 3100. (The patients in Study 3072 were 4-8 years old.)

Figure 4

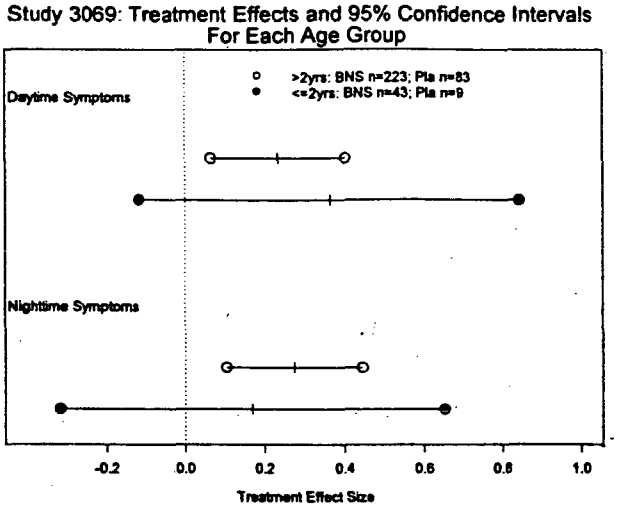
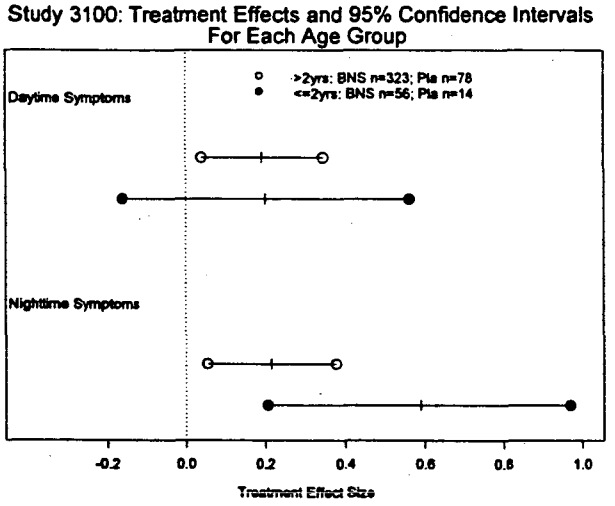


Figure 5



Reviewer Comment

Recall that the diary cards of the older children were presumably filled out by the patients themselves, whereas the diary cards of the younger children were not. Despite this factor, it appears that the treatment effects were similar for the different age groups. The treatment effect of nighttime symptoms was actually numerically (but not statistically significantly) greater among the younger patients in Study 3100 than in the older patients. This effect was not seen in Study 3069.

Inhaled Steroid Use Prior to Randomization

In Study 3100, 145 (30.8%) of the patients were on inhaled steroids up to randomization. The patients not on inhaled steroids prior to randomization improved more than those on inhaled steroids, even among the placebo groups for both nighttime and daytime symptoms.

Table 6: Study 3100 Mean Changes from Baseline (not adjusted for Center Effect)

	Placebo 92	0.25 mg QD 93	0.25 mg BID 97	0.5 mg BID 96	1.0 mg QD 93
Nighttime					
-No Inhaled Steroids	-0.25	-0.28	-0.53	-0.50	-0.40
-Inhaled Steroids*	0.08	-0.28	-0.39	-0.18	-0.39
Daytime					
-No Inhaled Steroids	-0.34	-0.26	-0.47	-0.57	-0.40
-Inhaled Steroids*	-0.01	-0.44	-0.32	-0.28	-0.37

* Prior to randomization

1.5 Conclusions

The applicant submitted three placebo-controlled 12-week studies (Study 3072, n=178; Study 3069, n=359; Study 3100, n=481) to support the claim that budesonide nebulizing suspension is safe and effective in reducing the symptoms of asthma in children ages [redacted] to eight years. A four-point rating scale was used to assess nighttime and daytime symptoms, separately. In these studies reductions in nighttime symptoms ranged from -.08 to -.16 units for placebo and -.36 to -.49 units for active drug. The reduction in daytime symptoms ranged from -.11 to -.26 units for placebo and -.37 to -.57 units for active drug. Study 3069 continued as an open-label safety study for an additional year (Study 3069b).

The studies were designed to demonstrate that BNS is efficacious for both nighttime and daytime symptoms. Therefore, statistical significance on both nighttime *and* daytime symptoms was necessary for the results of a treatment group to be declared statistically significantly different from placebo. (However, a multiple comparisons adjustment was needed to make the three -Studies 3069 & 3072- and four -Study 3100- comparisons between the various doses and placebo in each study. The Step-Down Procedure could not be used in Study 3100 because there were two dosing regimens that yielded the same total daily dose. The sponsor chose not to specify any multiple comparisons procedure before breaking the blind.) The results of the studies should be examined cautiously because there is an increased likelihood of statistical significance when making multiple comparisons between each dose and placebo. Overall, the results of the studies appeared to demonstrate efficacy of the BID dose groups only. There was no apparent increase in efficacy with increasing dose above the .25 mg BID dose in any of the studies.

Studies 3069 and 3100 included a total of 122 patients less than two years old (99 of these were on BNS). The treatment effects for the patients 2 years and younger were similar to those above two years for both daytime and nighttime symptoms in both studies.

After patients completed the 12-weeks of double-blind treatment period in Study 3069, they had the option of continuing in the open-label phase (called Study 3069b), if they met entrance requirements. 89% of patients continued. A review of Study 3069b is presented in the following section on safety.

2. Safety

2.1 Adverse Events

Safety evaluations included clinical laboratory results, physical examinations and adverse event reporting.

There was no obvious relationship between dose of budesonide and percent of patients reporting adverse events in any of the three placebo-controlled studies (see Table 7 below). The incidence of adverse events was similar between the two treatment groups in the open-label extension of Study 3069, called Study 3069b. The percentages of patients with at least one moderate or severe adverse event were similar across treatment groups as well.

Table 7: Summary Table of Percent of Patients who had at least one Adverse Event

Study	Placebo	.25 mg QD	.25 mg BID	.5 mg QD	.5 mg BID	1.0 mg QD	1.0 mg BID	Total Active
3069	88	84		85		86		85
3072	86		83		86		80	83
3100	84	82	90		85		86	86
	Conven-tional	BNS						
3069b	94	95						

The sponsor also presented results of proportional hazards model analyses for the one-year open label study in order to take "time on study" into account when calculating the relative risk for each adverse event. The average number of days the patients were in the open-label study was 342, (median = 364; range = 47- 424). None of the relative risks indicated a statistically significantly greater risk for the BNS group. The relative risks of two events (pneumonia and abdominal pain) indicated a statistically significantly greater risk for the conventional treatment group. Neither the sponsor nor the reviewing medical officer had an physiological explanation for these findings.

2.2 Study 3069b

Study 3069b was a 52-week open-label extension of Study 3069 designed to assess safety factors. One of the primary questions it addressed was whether BNS use was associated with growth impairment in children. This study suggested that BNS may have affected the growth velocity at a rate of approximately 0.76 - 0.85 cm/year, however, the findings should be regarded in the context of several problems inherent in the study design (i.e., unblinded treatments, self-selection into the study, previous use of study drug with no washout period, analyses not pre-specified in protocol), as well as a confounding factor related to the study conduct (differential prednisone use).

2.2.1 Design

2.2.1.1 Introduction

The sponsor submitted Study 3069b, an open-label safety study, to support the claim that BNS does not impair growth rate in children. Study 3069b immediately followed Study 3069, the double-blind placebo-controlled study. There was no washout period between the double-blind and open-label phases. The patients on placebo and BNS doses in Study 3069 were re-randomized in a 2:1 fashion to maintenance levels of BNS (starting at .5 mg QD) and Conventional treatment (including beta2-agonists, methylxanthines, and inhaled non-steroidal anti-inflammatory agents, but not inhaled glucocorticosteroids) for the open-label study. The percentage of patients randomized to BNS in the open-label phase who had previously been on BNS (74%) was similar to that of patients randomized to Conventional treatment (79%), see Table 8 below.

Table 8: Number and Percent of Patients in each Open-Label Phase treatment group who had previously been assigned to Placebo, .25 mg , .5 mg and 1.0 mg groups in Double-Blind Phase

Double-Blind Phase Treatment arm	Open-Label Phase	
	Randomized to BNS	Randomized to Conv
Placebo	47 (26%)	19 (21%)
.25 mg	49 (27%)	22 (24%)
.5 mg	43 (24%)	21 (23%)
1.0 mg	43 (24%)	28 (31%)
All BNS groups together	135 (74%)	71 (79%)

The design of the study is displayed in Figure 6 and includes the numbers of patients in each treatment group. Three-hundred fifty nine (359) patients were randomized into the double-blind phase. Eighty-seven of these patients did not continue in the open-label phase. The study report did not state how many of these patients were eligible to continue but chose not to, and how many were ineligible. The percentages of continuing patients were similar across treatment groups. The total number of patients re-randomized was 272. However, 9 of these patients dropped out the same day they were randomized (presumably after they found out to which treatment arm they had been assigned). Therefore, the final number of patients with data was 263. Seventeen more patients dropped out after only two visits.

Figure 6: Study Designs of Studies 3069 and 3069b