CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20750

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: SEP 22 1997

NDA#:	**20-750**
Applicant:	**Fisons/ Rhone-Poulenc Rorer Pharmaceuticals**
Name of Drug:	**Tilade Nebulizer Solution (nedocromil solution inhalation solution)**
Indication:	**Asthma**
Documents Reviewed:	**9-30-96 Vol. 1.1, 1.26-1.121; 2-10-97; 3-21-97; 5-28-97; 7-29-97**
Statistical Reviewer:	**B. Bono, M.S.**
Medical Input:	**B. Otulana, M.D.**

1. Summary of Studies

1.1 Introduction

The company submitted eight placebo controlled studies to support the efficacy of Tilade Nebulizer Solution. The sponsor described the studies as either symptom reduction or maintenance studies.

- The symptom reduction studies were designed to show a reduction in asthma symptoms among patients with moderate levels of asthma symptoms, in terms of both severity and frequency. There were five symptom reduction studies, of which four were adult (1408, 2333, 1409, and 1691) and one was pediatric (1574).

- The "maintenance" studies were designed to evaluate the clinical benefits of Tilade Nebulizer Solution in children with mild, episodic symptoms. Children in the "maintenance" studies were allowed to enter with little or no baseline symptoms. However, in order to observe children during a period of higher likelihood of acute exacerbations, only children who had a history of exacerbations during the fall-winter months were entered, and they were entered in a cohort fashion at the beginning of the season. There were three maintenance studies, all in the pediatric population (1978, 2233, and 3003).

The sponsor claimed that the results of Studies 1408, 1574, 2333, 1978 and 2233 provided evidence of the efficacy of Tilade Nebulizer Solution. This reviewer concluded that:

- The results from Symptom Reduction Studies 1408 (adult) and 2333 (adult), provide evidence that Tilade Nebulizer Solution QID reduces symptom scores in asthma patients.

- The results from Maintenance Study 2233 (pediatric) provide evidence that Tilade Nebulizer Solution TID increases the percent of symptom free days in children ages 2-5 with mild asthma.

- Results from Symptom Reduction Study 1574 (pediatric) provide *supportive* evidence that Tilade Nebulizer Solution QID reduces symptom scores in asthma patients.

- Results from Maintenance Study 1978 (pediatric) provide *supportive* evidence that Tilade Nebulizer Solution TID increases the percent of symptom free days in children ages 6-12 with mild asthma.

The results of Studies 1409, 1691, and 3003 did not provide statistically significant evidence of the efficacy of Tilade Nebulizer Solution, see Dr. Otulana's review. These studies are not included in this review.

1.2 Objectives

The objectives of the studies were to determine the safety and efficacy profile of Tilade Nebulizer Solution, or nedocromil sodium nebulizer solution (hereafter referred to as NSNS) as compared to the placebo for the treatment of asthma. The symptom reduction studies, (1408, 1574, 2333) were specifically designed to study the effect of NSNS in reducing the symptoms

of asthma. Studies 1978 and 2233 were designed to test the hypothesis that NSNS, "acts prophylactically to prevent symptoms occurring in mild/moderate asthmatics". Studies 1408 and 2333 were adult studies, whereas Studies 1574, 1978 and 2233 were pediatric studies.

1.3 Study Designs

The studies were placebo-controlled double-blind randomized, parallel designs in patients with asthma. All of the studies had two arms (placebo and NSNS). Studies 1408, 1574, and 2333 used qid dosing, whereas the two maintenance studies, 1978 and 2233, used tid dosing. Patients were randomized to receive treatment for 12 weeks in all of the studies, except Study 1978, where patients received treatment for 24 weeks.

Table 1: Primary Efficacy Studies

Study	Dates	Study Arms (dosing)	# of sites	duration of treatment	itt* n	Ages
		Symptom Reduction Studies				
1408	4/88 - 5/89	placebo NSNS 11mg QID	5	12 wks	123	Adult (18-70)
1574	3/90-2/91	placebo NSNS 11mg QID	7	12 wks	166	Pediatric (6-12)
2333	7/92- 5/93	placebo NSNS 11mg QID	8	12 wks	189	Adult (12-81)
		Maintenance Studies				
1978	9/89-5/90	placebo NSNS 11mg TID	7	24 wks	93	Pediatric (6-12)
2233	9/91-2/92	placebo NSNS 11mg TID	15	12 wks	279	Pediatric (2-5)

*ITT is the pure intent-to-treat population, i.e., all patients who were randomized to receive treatment.

The studies assessed asthma symptoms (daytime asthma severity, sleep difficulty due to asthma and cough), concomitant medication use, and pulmonary function (morning and evening PEFR, FEV_1, FVC, FEF_{25-75}, and PEFR). The severity of daytime asthma was graded on a scale of 0-4 in all studies. The severity of nighttime asthma (sleep difficulty due to asthma and cough) was measured on different scales in the studies.[1] Additionally, patients and physicians recorded global evaluations of therapeutic response.

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[1] The severity of the nighttime scores (sleep difficulty due to asthma and cough) was graded on a scale of 0-2 in Studies 1408, 2333 and 1978, and on a scale of 0-4 for Studies 1574 and 2233. The primary efficacy variable in Study 1574 was change from baseline of worst baseline symptom, thus the three symptoms --- daytime asthma, nighttime asthma, and cough --- had to be scored on the same scale.

The protocols of all five studies specified that the analysis of the primary variable would be "stratified non-parametric analysis of covariance of ranks" based on the efficacy populations.[2] A rank analysis is an analysis on the *ranks of the variable*, rather than the observed data. In meetings with the FDA prior to the submission of the NDA, the FDA requested that the sponsor also provide parametric analyses on the intent-to-treat (ITT) populations.

Reviewer Comment

The sponsor identified different protocol-specified analyses for each study. These differences included various primary efficacy variables, primary time periods of analysis, definitions of the efficacy population, definitions of failures, and imputation methods for missing values. The FDA requested parametric analyses on the primary efficacy variables using the ITT populations, a more standard approach than the proposed analyses, to evaluate the strength of the results across studies. The sponsor did not respond consistently to this request.

1.4 Efficacy Variables and Time Periods (Table 2)

The primary efficacy variables and primary time periods in the different studies varied. With the exception of Studies 1408 and 1978, the protocols of each of the five studies specified different primary efficacy variables.

Table 2: Primary Efficacy Variables and Time Periods

Study	Primary Time Period	Primary Endpoint
1408	final 8 weeks (Weeks 5-12)	mean of the ranks of the change in the *daytime asthma severity score* and *sleep difficulty due to asthma score*
1574	final 8 or 10 weeks (Weeks 3-12 or Weeks 5-12)*	mean of the ranks of change from baseline of worst baseline symptom
2333	final 10 weeks (Weeks 3-12)	mean of the ranks of the change of *summary score* (sum of daytime asthma and sleep difficulty) and *concomitant medication use score*
1978	all 24 weeks (Weeks 1-24)	mean of the ranks of the change in *the daytime asthma severity score* and *sleep difficulty due to asthma score*
2233	all 12 weeks (Weeks 1-12)	mean of ranks of change from baseline *percent of symptom free days (defined as any day on which patient scores a 0 for both daytime and sleep difficulty due to asthma and takes concomitant medications; β_2-agonsists allowed only if patients had symptoms)*

* The protocol specified the primary time period to be "the final 10 weeks" on page 17 and "the final 8 weeks" on page 24. The study report stated that the primary time period was the final 10 weeks of the double-blind treatment period.

[2] For each patient, the change from baseline of each symptom in the symptom complex is calculated. Within each clinic, for each symptom, the scores are ranked according to magnitude of change from baseline, and the ranks are standardized based on clinic sample size. For each patient, the standardized ranks of each symptom in the symptom complex are averaged. Statistical comparisons are combined across centers through the extended Mantel-Haenszel procedure, while utilizing the information in baseline data as a covariate.

1.4.1 Efficacy Variables

The primary efficacy variables as specified in the protocols were,

- the change from baseline summary symptom score – daytime plus nighttime asthma (Studies 1408 and 1978)[3],
- the change from baseline of the worst baseline symptom score (Study 1574),
- a combined score: the change from baseline summary symptom score (daytime plus nighttime asthma) and the concomitant medication use score (Study 2333), and
- the change from baseline percent of symptom-free days (Study 2233).

Symptom Reduction Studies

The rationale for the sponsor's choice of "worst baseline symptom" as the primary efficacy variable for Study 1574 is described below, and defined more precisely on page 26.

> "Recognizing a wider variance in the manifestation of asthma in children, the entry criteria for the symptom reduction study in children (CR1574) were based on the severity and frequency of any one of the symptoms (daytime symptoms, nighttime symptoms, and cough) during baseline. The most predominant symptom thus identified during baseline (referred to as 'worst symptom') and by which a patient was qualified for entry should be more responsive to intervention than the total symptom score. Therefore, "worst symptom" was selected *a priori* as the primary efficacy variable for this study."
>
> Page 8-110-44 of NDA

In the protocol for Study 2333 the sponsor chose a combined score that placed "equal emphasis" on the summary symptom score and the concomitant asthma medication score. The efficacy of NSNS was to be established based on a single statistical test (rank analysis) that combined both variables.

Maintenance Studies

The first maintenance study, 1978, used the same efficacy variable as the first symptom reduction study, 1408. However, the results of Study 1978, based on this variable, were not statistically significant. In an addendum of the study report, the sponsor proposed that in this study population of mild to moderate asthmatics, maintenance of symptom free time was a relevant measure of the efficacy of an asthma therapy.

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[3] The protocol defined the primary ***objective*** of Study 1978 to be "bronchial hyperactivity secondary to respiratory infections...measured by the results (PD_{20}) of a profile of methacholine challenge tests performed three days, three weeks and six weeks after the onset of a documented respiratory infections". However, the primary efficacy ***variable*** was defined in the protocol as "the symptom complex of daytime asthma severity and sleep difficulty due to asthma" over the primary time period defined as weeks 1-24. The study report reiterated these definitions. However, the integrated summary of efficacy stated that the primary efficacy variable was PD_{20} post SRI episodes. This review assumes the primary efficacy variable was the summary symptom score as defined in the protocol and the study report. The results of the analyses of PD_{20} are presented in section 2.6.6, Secondary Efficacy Variables, page 30.

"As the milder asthmatic children tend to display a more episodic character to their symptoms, the patients in this study on the average were free of daytime symptoms or sleep difficulty due to asthma for six days out of the 14-day baseline period. In such a population, it appears that the therapeutic utility of an anti-asthmatic agent can be better assessed by its potential in reducing the frequency of episodes of major and minor exacerbations due to specific SRI [symptomatic respiratory infection], and non-specific triggers and consequently in maintaining or increasing the symptom free days."

Page 8-60-16 of NDA

Thus, percent of symptom free days was analyzed (*post-hoc*) in Study 1978. Study 2233, another maintenance study and the third pediatric study, enrolled younger patients, ages two to five, and specified in the protocol that the primary efficacy variable was change from baseline percent of symptom-free days. The protocol specified that a symptom-free day was a day on which the patient had no daytime asthma, nor sleep difficulty due to asthma. No oral steroid was used during symptom free days. The protocol also stipulated that the patients were to use β_2-agonists only if they had symptoms.

Reviewer Comment

The post-hoc *analysis of Study 1978 was chosen for Study 2233 during the design phase. As will be seen in Section 2.6.4, page 27, the results of the* post-hoc *analysis of Study 1978 were well replicated by Study 2233.*

1.4.2 Time Periods

The sponsor chose different portions of the treatment periods to be the "primary time period of efficacy evaluation" in the studies. The rationale for the sponsor's choice of time periods was discussed in the NDA.

"...Potential clinical benefits of nedocromil sodium may be derived from a short term effect of protection against several stimuli after dosing and a long term effect of reduction in hyperreactivity which may take four weeks to reach a significant magnitude. For this reason it was originally believed that, in order to assess the full benefit of the treatment, the primary test should be based on the time period after the initial four weeks of treatment. This was the basis of selecting treatment Weeks 5 to 12 as the primary time period for efficacy evaluation in Studies CR1408, CR1409 and CR1691. The results of Study CR1408, however, subsequently showed that the onset of significant clinical benefits in symptom reduction was earlier than four weeks and for subsequent symptom reduction studies CR1574, and CR2333, treatment Weeks 3 to 12 was selected as the primary time period for efficacy evaluation in the protocol.

For maintenance/prophylaxis studies, the comparison of symptom free days between the active treatment and placebo was based on the entire treatment period (12 weeks for CR2233 and CR3003 or 24 weeks for CR1978). An evaluation of the magnitude of symptom reduction was also made in these studies with the focus on the symptom level during treatment Weeks 5 through 12."

Page 8-110-45 of NDA

In summary, the "primary time periods" were weeks 5-12 for Study 1408 and weeks 3-12 for Studies 1574 and 2333. The primary time periods for the "maintenance" studies included the full treatment periods (weeks 1-24 for Study 1978 and weeks 1-12 for Study 2233).

Reviewer Comment
The protocol for Study 1574 specified the primary time period to be "the final 10 weeks of the study" (weeks 3-12) on page 17 and "the final 8 weeks during double-blind treatment" (weeks 5-12) on page 24. The study report acknowledged this discrepancy and stated that the primary time period was the final 10 weeks of the double-blind treatment period.[4] This review assumes the protocol-correct primary treatment period was Weeks 3-12.

The secondary efficacy variables were daytime asthma, sleep difficulty due to asthma, cough severity, morning PEFR, evening PEFR, concomitant medication use, FEV_1, FVC, FEF_{25-75}, PEFR, Physician's Assessment of Asthma, Physician's Opinion at End of Study, Patient's Opinion at End of Study. In Studies 1978 and 2233, an additional objective was to assess whether treatment with NSNS improves the patient's response to short courses of oral steroids administered to control deterioration in asthma symptoms secondary to upper respiratory infections (URI). A summary asthma symptom score during the 14-day period after the start of oral steroids was also included as an endpoint.

2. Results

2.1 Compliance

Compliance was monitored using daily diaries. The electronic data submission for the symptom reduction studies included a variable that measured the number of doses of study drug a patient took per day. As a measure of compliance, this reviewer calculated descriptive statistics of this variable averaged over the primary treatment period times, (Table 3). Recall, the dosing regimen of the symptom reduction studies was qid. The treatment groups appear to be similar in terms of average study drug usage.

Table 3: Study Drug Usage (number of doses per day)

Study (Period)	Treatment	n	Mean	Std Dev	Min	Max
1408	Placebo	46	3.76	0.34	2.59	4.00
(Weeks 5-12)	NSNS	47	3.85	0.17	3.30	4.00
1574	Placebo	82	3.80	0.25	2.76	4.00
(Weeks 3-12)	NSNS	78	3.82	0.31	1.64	4.00
2333	Placebo	83	3.82	0.25	2.53	4.01
(Weeks 3-12)	NSNS	87	3.80	0.30	2.58	4.00

The protocol of Study 2333 indicated that additional efficacy analyses would be performed excluding non-compliant patients if the percentage of non-compliant patients

[4] The results and conclusions were similar using the FDA-requested parametric analysis of covariance.

was more than 5%. Only 2.7% of the patients were classified as non-compliant, thus no additional statistical analysis was performed excluding these patients.

The maintenance studies (1978, 2233) appeared to have acceptable compliance. The data were not submitted electronically.

Reviewer Comment
Overall, it appears that compliance was balanced across treatment groups and the numbers of patients with poor compliance were small. Thus, it is assumed that issues related to compliance did not seriously affect the results of these studies.

2.2 Patient demographics
With the exception of gender imbalances in Studies 1408 (p=0.063) and 1978 (p=0.039), the treatment groups were comparable with regard to demographic and disease characteristics (Tables 4 and 5). In these studies the placebo groups had a higher percentage of males. Race was only collected in Studies 2333, 2233 and 3003[5], (Table 6).

Table 4: Demographics

	Race		Age mean range		Sex		Duration of Asthma (years) mean range	
Study	Placebo	NSNS	Placebo	NSNS	Placebo	NSNS	Placebo	NSNS
1408	Not Available	Not Available	36.8 13-70	35.0 13-64	73% Male	57% Male	20.0 1-54	17.9 1-50
1574	Not Available	Not Available	9.1 6-12	9.5 6-12	72% Male	77% Male	5.7 1-12	6.1 1-12
2333	91% Caucasian	90% Caucasian	34.1 12-69	31.5 12-81	50% Male	60% Male	17.2 2-57	16.1 1-52
1978	Not Available	Not Available	9.2 6-12	8.8 6-12	73% Male	52% Male	6.0 1-12	5.7 1-12
2233	83% Caucasian	82% Caucasian	3.5 1.9-5.0	3.5 1.9-5.0	66% Male	64% Male	2.0 0.5-4.9	2.0 0.5-4.5

Gender
Reviewer Comment
The effect size (the difference between active and placebo treatment) in total asthma symptom scores (the sum of daytime symptoms, sleep difficulty and cough) in the male and female subgroups was examined by the sponsor to detect any major disparity in treatment response between the two gender groups. The data from all symptom reduction studies with a qid dose regimen were pooled. Similar analyses were done for the pooled data from all maintenance/prophylaxis studies with a tid dose regimen. Results of these analyses revealed no evidence of gender specific differential treatment effects.

[5] In Study 3003, the placebo group was 86% Caucasian and the NSNS group was 89% Caucasian.

Table 5: Gender Imbalances

Study	Placebo		NSNS		*p*-value
	Males	Females	Males	Females	
1408	44 (73%)	16 (27%)	33 (57%)	25 (43%)	.063
1574	60 (72%)	23 (28%)	61 (77%)	18 (23%)	.478
2333	47 (50%)	47 (50%)	56 (60%)	38 (40%)	.241
1978	33 (73%)	12 (27%)	25 (52%)	23 (48%)	.039
2233	91 (66%)	46 (34%)	85 (64%)	47 (36%)	.587

Race

The representation of non-caucasian patients in the three studies in which race was collected ranged from 9-17%. The sponsor did not perform separate evaluations of efficacy or safety.

Table 6: Frequency (Percent) of Race by Study

Race	Study		
	2233	2333	3003
American Indian	2 (0.6)	0 (0.0)	2 (0.6)
Hispanic	11 (3.4)	10 (3.8)	4 (1.2)
Black	27 (8.4)	11 (4.2)	34 (10.6)
Asian	4 (1.2)	3 (1.1)	0 (0.0)
Other*	10 (3.1)	0 (0.0)	2 (0.6)
Caucasian	268 (83.0)	238 (90.9)	279 (86.9)
Total	323	263	321
Missing	1	1	3

* Other includes categories that were identified by the sponsor as: "Mixed", "Mulato", "White/Black", or "½ Black".

2.3 Patient Accountability

The tables in the NDA regarding randomization sample size and "efficacy" sample sizes were inconsistent. Table 7 below identifies the inconsistencies found in the NDA submission.

Table 7: Inconsistencies Regarding Patient Accountability

Study	Trt group	number randomized (from ISE and ISS)	number randomized (from individual study report)	n included in safety analyses* (from ISE and ISS)	n included in efficacy analyses (from ISE)	n included in efficacy analyses** (from individual study reports)	
Symptom Reduction Studies							
1408	Placebo	63	61	63	60	55	
	NSNS	60	62	60	58	58	
1574	Placebo	85	same	83	83	79	
	NSNS	81	same	80	79	76	
2333	Placebo	95	same	94	92	86	
	NSNS	94	same	94	94	89	
Maintenance Studies						Mean Scores	% Sx-free days
1978	Placebo	45	same	45	45	38	45
	NSNS	48	same	48	48	43	47
2233	Placebo	141	same	140	137	136	139
	NSNS	138	same	136	132	134	134

* patient had at least 1 dose of treatment

** patient had more than half of primary treatment period data available

Inconsistencies

1. The numbers of patients in Study 1408 randomized to the different treatment groups were reported as, placebo n=63 and NSNS n=60, in the Summary of Safety and Efficacy and as, placebo n=61 and NSNS n=62, in the individual study report. The electronic data that the company submitted to FDA are consistent with the individual study report.

2. The number of patients included in efficacy analyses was defined in the protocols and individual study reports as "the number of patients that had data for at least half of the primary treatment period time". The efficacy population in the Summary of Safety and Efficacy was not explicitly defined, and labeled only as "Efficacy Data Available". The numbers did not agree in any of the studies. The electronic database was consistent with the individual study reports.

3. The number of patients in the efficacy analyses of the maintenance studies (1978, 2233) were different, depending on the outcome variable analyzed. These studies were analyzed using the differences in percent of symptom free days in addition to the traditional mean differences in summary symptom scores between the two treatment groups.

   The sponsor did not calculate baseline and treatment period summary symptom scores for patients who had missing values for more than half the time period. However, the variable "percent of symptom-free days" *was* calculated for these patients. Thus, the numbers of patients with data for differences in percent of symptom free days were greater than those with data for differences in mean symptom scores (even at baseline, see Table 8).

Reviewer Comment

The numbers of patients in tables of Studies 1978 and 2233 in the individual study reports and integrated summary of safety and efficacy were identified as the "efficacy data available" or "efficacy population". The numbers were inconsistent across tables due to the different outcome variables analyzed. The sponsor addressed the concerns of this reviewer in a facsimile (dated July 30, 1997).

4. At meetings prior to the submission of the NDA, the FDA requested that the applicant perform analyses using the intent-to-treat population. ITT analyses were performed for Studies 1408, 1574, and 2233, but not Studies 2333 and 1978. In a response to FDA inquiries (dated July 30, 1997), the sponsor states that for Study 1978, only one NSNS patient was excluded from the analysis of the percent of symptom free days because no baseline data were recorded, and, "For Study 2333, as documented in Section 9.1 of the study report, only three patients were excluded from the efficacy analyses. Two of these patients did not provide any data after randomization and one provided data for only one day of the double-blind treatment period. Given this, the intention to treat analysis in this study was essentially the analysis presented in the report."

Reviewer Comment

Section 9.1 of the study report further states that, "Hence, 186 patients were included in the efficacy analysis: 94 in the TILADE group and 92 on Placebo. The actual number of patients for any particular analysis depends on the number of patients having non-missing data for that variable." The results of the analysis of the primary efficacy variable during the primary time period were presented in Section 9.2.1.3 of the NDA. The sample sizes reported for each treatment group were 89 in the TILADE group and 86 in the placebo group. Thus, in addition to the three patients the sponsor identified in the response, eleven more were excluded in this analysis. Also, the FDA-requested, parametric analyses using, 1) last observation carried forward (LOCF), and 2) worst score on the scale carried forward (WSCF), found in an appendix of the study report, included only 175 of the 189 randomized patients. Consequently, the analyses requested by the FDA only included those patients who either 1) completed at least half of the daily diary cards for the variable being analyzed, or 2) were considered failures with data imputed forward.

Intent-to-treat analyses could not be performed by the reviewer for Study 2333, because the electronic datasets that the sponsor submitted did not have the daily diary data, only averages of two week periods (Weeks 1-2, Weeks 3-4, etc.), and averages of the primary time period (i.e., Weeks 5-12). The averages of each time period only had data for patients that had values for greater than or equal to half the time period.

5. Study 1408 had one patient who enrolled twice. He was randomized to NSNS both times. This patient enrolled as patient 12 with his first visit on July 18, 1988. After two weeks of treatment, on August 29, 1988, he was reported as lost to all follow-up and was withdrawn from the study. On December 2, 1988, this patient had enrolled in the study again, and was assigned patient number 23. This time he completed the study. At the time of the NDA submission, the applicant did not know that this

patient enrolled twice. At the request of the FDA, the company confirmed through case report forms and consent signatures, that the two patient numbers referred to the same individual.

Reviewer Comment

Analyses were performed with data excluding the first, the second, and both records for this patient. These re-analyses did not affect the conclusions of the study. In addition, an analysis was performed excluding the entire clinic (Dr. Steinberg) that allowed this patient to enroll twice (see Appendix A). Treatment effect was statistically significant (p=0.0499) in this analysis. It appears that the exclusion of the clinic from the analyses did not alter the conclusions.

Reviewer Comment

Overall, the observed inconsistencies were prevalent at low levels and balanced across treatment groups. Therefore, they did not appear to seriously affect the conclusions of the studies.

Table 8 summarizes patient activity in more detail.[6] This table describes the reasons why patients were excluded from the efficacy analyses. A small percentage of patients had no baseline data (0.7%-2.1%), but the majority of the exclusions were due to patients having less than half the treatment period data (1.4%-9.8%).

Table 8: Patient Accountability

Study	Variable	Treatment Group	Randomized to treatment	No Baseline Period Data	No Treatment Period Data[1]	"Efficacy" population	Total Sample Size		
							Randomized	"ITT"	Efficacy
1408	Mean of Symptoms	Placebo	61		6	55			
		NSNS	62		4[2]	58	123	120	113
1574	Mean of Symptoms	Placebo	85		6	79			
		NSNS	81		5	76	166	163	155
2333	Mean of Symptoms	Placebo	95		9	86			
		NSNS	94		5	89	189	NA	175
1978	Mean of Symptoms	Placebo	45		7	38			
		NSNS	48	1	4	43	93	NA	86
	% Sx-free days	Placebo	45			45			
		NSNS	48	1		47	93	NA	92
2233	Mean of Symptoms	Placebo	141	2	3	136			
		NSNS	138	1	3	134	279	NA	270
	% Sx-free days	Placebo	141		2	139			
		NSNS	138	1	3	134	279	273	273

NA The company did not submit ITT analyses.

1 A patient did not have any treatment period data for the primary efficacy variable if s/he 1) withdrew due to reasons other than treatment failure, and 2) had data for less than half the treatment period time.

2 Patients #12 and 512 in Study 1408 refer to the same individual. This patient enrolled twice. See Section 2.3, for more details.

[6] The numbers of the ITT population sample sizes were extracted from the applicant's study reports, not the electronic database.

2.4 Withdrawals, Treatment Failures and Imputation Methods

2.4.1 Withdrawals

The sponsor's definition of withdrawals overlapped the definition of treatment failures. Patients who withdrew due to lack of effect were considered both withdrawals and treatment failures. Patients who withdrew due to adverse events or reasons unrelated to treatment were identified as withdrawals, but not failures. Thus for completeness, Table 9 below includes withdrawals, failures (who withdrew) and failures who remained in the study but took disallowed concomitant medication.

Table 9: Withdrawals and Failures (defined in section 2.4.2)

	NSNS						Placebo					
		Withdrawals						Withdrawals				
		Disall Meds	Lack of Eff	Other[1]				Disall Meds	Lack of Eff	Other[1]		
Study	N	Failures		AE	UTT	Total (%)	N	Failures		AE	UTT	Total (%)
1408	60/62[2]	7	0	2	2	11	63/61[2]	3	0	3	4	10
1574	80	10	1	6	5	22 (28)	83	11	0	3	3	17 (20)
2333	94	11	1	5	2	19 (20)	94	19	0	7	5	31 (33)
1978	48	7	0	5	4	16 (33)	45	7	0	3	6	16 (36)
2233	136	0	0	4	8	12 (9)	140	5	1	4	9	19 (14)
Total	418/420	35	2	22	21	80	425/423	45	1	20	27	93

1 Other: refers to patients who withdrew for reasons other than lack of effect, i.e. adverse events and events "unrelated to treatment".

2 The data in this table were extracted from three sources: the integrated summaries of safety and efficacy, the individual study reports and the electronic database. The number of patients randomized for Study 1408 does not correspond with that reported in the study report or the database for Study 1408 (see Table 7). Both sample sizes are reported in this table, Table 9. Percentages for Study 1408 and the studies combined are not calculated because of the discrepancy.

2.4.2 Treatment Failures

In the symptom reduction studies, the patients who either, 1) did not complete the studies for lack of treatment effectiveness, or 2) took disallowed concomitant medications, were considered "failures". The maintenance studies had exceptions to this definition based on why the concomitant medication was being used. The details are described in the section outlining the imputation methods.

Reviewer Comment

In the study report of Study 1978, the definition of a failure was changed and 15 failures in the NSNS group and 17 failures in the placebo group were either treated as "completers" or classified as "temporary treatment failures". Study 2233 essentially duplicated this new definition in the protocol and had fewer patients classified incorrectly post-hoc.

2.4.3 Imputation Methods

In the parametric analyses, the data of failures who withdrew were imputed from the time of withdrawal to the end of the study. For the failures who took more than the allowed amount of concomitant medications, the data were imputed from the time the patient exceeded the allowable limit.

In the non-parametric analyses, patients who were considered failures were assigned ranks based on time of failure. The failures were given the worst possible ranks compared to the non-failures based on time to failure. In the non-parametric analyses stratified by clinic, the failures were given the worst possible ranks within a given clinic based on time to failure.

The data of patients who withdrew from the studies for reasons other than lack of effect (i.e., lost to follow-up, adverse event) were used to the point of withdrawal (as per protocol).

Imputation Method: Studies 1408, 1574, 2333

The protocols of the symptom reduction studies (1408, 1574, 2333) and one of the maintenance studies, Study 1978, specified the method for imputing missing values of asthma symptoms to be the Worst-Score-on-the-scale-Carried Forward (WSCF). At meetings prior to submission of the NDA, the FDA requested that the applicant perform analyses using the last value the patient recorded before failing (Last-Observation-Carried-Forward, LOCF). The applicant submitted these analyses, and electronic data with the data already imputed using LOCF, for Symptom Reduction Studies 1408, 2333, and 1574 for either the protocol-correct or the *post-hoc* rank analysis (or in some cases both). Thus, all analyses for the former three studies presented in this review were done using LOCF for patients considered failures. However, neither the study reports, nor the electronic data of Maintenance Study 1978 indicate LOCF was used. Study 2233 did not use the scores of asthma symptoms to evaluate the efficacy of Tilade, thus, a different method of imputation was used. The methods used for Studies 1978 and 2233 are described below.

Reviewer Comment

It was not always clear which method of imputation was used. The tables and output were not consistently labeled by method.

Imputation Method: Study 1978

In the protocol and the study report failures were defined as patients who 1) withdrew from the study early and noted ineffective treatment as reason for withdrawal or 2) took oral or inhaled corticosteroids to treat a severe exacerbation of asthma symptoms. Data beyond that point was used as recorded. Children who took a short course of oral corticosteroids to treat an *acute* exacerbation were considered "temporary treatment failures". For those children considered temporary treatment failures, the worst score on the scale was imputed for two weeks after the start of use of any corticosteroids. Scores

during weeks 3 and 4 following initiation of corticosteroids were considered "missing" values.

Reviewer Comment
In an addendum to the study report, where the variable "percent of symptom free days" was first defined and analyzed, the definition of treatment failures was changed depending on whether or not the child used the corticosteroids for an asthma exacerbation associated with a symptomatic respiratory infection (SRI). The new definition was used, along with the new primary efficacy variable "percent of symptom free days" in the protocol of Study 2233.

Imputation Method: Study 2233
Patients were classified (as per protocol) as treatment failures if they were withdrawn from the study prior to the completion of the 12 week treatment due to intolerable asthma symptoms or ineffective study medication as determined at the final patient interview or if they required disallowed asthma medications, including chronic use of oral corticosteroids, for symptom control during the study. Data of treatment failures were imputed or adjusted after the point of failure using the following method to reflect this outcome. The asthma symptom(s) which caused the patient to be classified as a treatment failure were assumed to take the worst value on the scale from the point of failure through the end of the 12 week treatment period. For the other symptoms, the last recorded score was carried forward for the remaining treatment period. For computing symptom free days, the entire period after the point of failure was considered days with symptoms.

The protocol stated that if a patient had a confirmed URI then the patient could be given up to 14 days of prednisone and remain in the study. If a patient was given prednisone without a confirmed URI, then the patient would be considered a failure and the symptom scores adjusted as described above.

Six children were given prednisone for 14 days without a confirmed URI and the sponsor considered these patients "temporary treatment failures", in violation of the protocol. Their symptom scores were adjusted (to the worst score on the scale) for the 14 days that they were on the prednisone. Per protocol, they should have been considered failures and had their scores adjusted for the remainder of the study.

Reviewer Comment
Five of the six children that were labeled "temporary treatment failures" instead of "treatment failures", as per protocol, were on the placebo arm. Thus, by using the scores as recorded after 14 days, if there were any residual effects, the size of the estimate of the treatment effect would actually be smaller than had the sponsor followed the protocol and adjusted the scores for the rest of the study.

Six additional children were considered "failures", (five used disallowed medications and one dropped out due to lack of effect). All six children were on the placebo arm. The days after the point of failure were counted as "days with symptoms" in the analysis of

*Percent of Symptom Free Days. The assumption that the children would have continued to experience "some symptoms" for the entire length of the study may not be realistic in this mild, episodic population. Another plausible method would be to calculate the variable using only those days before the patient failed. For example, the calculation of Percent of Symptom Free days for a patient that was on the study for 20 days and was symptom-free 6 of those 20 days would be : 6/20*100=30%. The calculation using the sponsor's method would be 6/84*100=7%. Since all six failures were on the placebo arm, the company's method favored NSNS. However, these six children represent only 2% of the total sample size, therefore it did not appear that this bias seriously affected the study conclusions.*

2.5 Adverse Events

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

Table 10: Percentage of patients reporting at least 1 adverse event

Study	Placebo	NSNS	Total N (exposed to study medication)
1408	39 (62%)	32 (53%)	123
1574	64 (77%)	58 (73%)	163
2333	84 (89%)	85 (90%)	188
1978	36 (80%)	43 (90%)	93
2233	129 (92%)	130 (96%)	276

Studies 2333, 1978 and 2233 had the highest percentages of patients reporting at least 1 adverse event. It is important to note that Study 1978 was twice as long as the others and it would be expected that the patients in this study would have a higher incidence of adverse events. In interpreting the event rates, it is also notable that Study 2233 had a young age group (2-5 years) and upper respiratory infections were the most common adverse event reported during the study period (placebo: 70%, NSNS:69%), contributing to this study's high event rate.

In all double-blind, placebo-controlled studies of NSNS, taste perversion (unpleasant taste), dry mouth and diarrhea were common (frequency ≥ 1%) adverse events reported at a statistically significantly higher frequency in the NSNS group.

Table 11: Percent of Patients Reporting Taste Perversion, Diarrhea and Dry Mouth in All Double-Blind, Placebo-Controlled Studies of NSNS

Adverse Event	Placebo n=933	NSNS n=936	*p*-value*
Taste Perversion	1.61	4.59	0.0001
Diarrhea	1.71	3.42	0.0099
Dry Mouth	0.32	1.18	0.0162

* One-sided *p*-value from a Fisher's Exact test.

Reviewer Comment

The fact that more NSNS patients noticed a bad taste to the treatment indicates that perhaps some patients were unblinded. It is possible that investigators may have noticed a predominance of reported taste perversion among half their patients. Some of the investigators were in more than one study; Drs. Bronsky, Galant, Geller, KM. Ellis, Pearlman, and Welch were each in two studies, and Dr. Kraemer was in three studies. The following table lists the frequencies of the three adverse events listed above within each of the five studies presented in this review. It appears that there were only a few cases of taste perversion per study.

Table 12: Incidences of Taste Perversion, Diarrhea and Dry Mouth

Study	Treatment Group	Taste Perversion n (%)	Diarrhea n (%)	Dry Mouth n (%)
1408	Placebo	1 (2)	0 (0)	2 (3)
	NSNS	2 (3)	2 (3)	3 (5)
1574	Placebo	2 (2)	2 (2)	0 (0)
	NSNS	6 (8)	2 (3)	0 (0)
2333	Placebo	2 (2)	2 (2)	0 (0)
	NSNS	6 (6)	3 (3)	1 (1)
1978	Placebo	1 (2)	0 (0)	0 (0)
	NSNS	3 (6)	0 (0)	0 (0)
2233	Placebo	2 (1)	5 (4)	0 (0)
	NSNS	5 (4)	13 (10)	1 (1)

2.6 Results of Analyses

2.6.1 Introduction

There were numerous problems with the way the applicant presented the results in the submission. These problems included, for example, sparsely detailed tables and contradictory sample sizes across tables. Furthermore, the sponsor did not submit the raw data electronically -- only the averages of symptom scores of two-week periods and the primary time periods (with data imputed) were submitted. The averages of the time periods had data for those patients with values for greater than or equal to half the time period. Thus, no ITT analyses, other than those produced by the sponsor, could be presented in this review.

The sponsor used a number of analytical methods, imputation rules and sample populations in producing the reported results. Three methods of analysis were employed: stratified rank-transformed analyses, Conover and Iman rank-transformed analyses, and parametric analyses. In general, two different methods of imputation were used by the applicant for each study, the protocol specified imputation method (Worst-Score-on-the-scale-Carried-Forward, WSCF) and the FDA-requested imputation method (Last-Observation-Carried-Forward, LOCF). For each of the two methods of imputation, the

three methods of analysis were performed. In addition, each of the analyses were performed on both the efficacy population and the ITT population in most of the studies.

Each analysis was reported with only some of the details necessary to identify it. Both the tables and computer output were sparsely detailed. In general, the results were difficult to identify and interpret. For example, some tables reported means of the symptom scores adjusted for baseline and center from a parametric analysis (labeled only as 'adjusted means') along with *p*-values from a non-parametric analysis.

In order to present means and standard deviations of the data for this review with descriptions of how they were calculated (i.e., efficacy or ITT population, LOCF or WSCF, unadjusted or adjusted for baseline and investigator, etc.), unadjusted means from the electronic database (efficacy population, imputation methods as described in section 2.4.3) were calculated and are presented in Table 14 and graphed in Figures 1-3.

To present the results for cross study comparison, the protocol-specified analyses and *post-hoc* parametric analyses based on the ITT populations (when available) using LOCF imputation are presented in this review. These *post-hoc* analyses used the protocol-specified primary efficacy variables and time periods.

Study results are presented in the following sections:

- Graphs of the averages of the summary symptom scores (daytime and nighttime asthma) of the symptom reduction studies provided as a general overview of the study results (section 2.6.2);
- The sponsor's results of the protocol-correct and *post-hoc* non-parametric analyses on the primary efficacy variables and time periods (section 2.6.3);
- The sponsor's results of the *post-hoc* parametric analyses on the primary efficacy variables and time periods (section 2.6.4);
- Center differences for Studies 1574, 1978 and 2233 (section 2.6.5); and
- Results of the secondary efficacy variables (section 2.6.6).

2.6.2 Summary Symptom Score Means

Biweekly means of the summary symptom scores (daytime asthma plus sleep difficulty due to asthma) by completion status are presented for the symptom reduction studies in Figures 1-3. The means labeled "failures" are for patients that were identified as treatment failures in the sponsor's electronic database. The means labeled "completers" are for patients that were identified as "include in safety and efficacy" in the sponsor's database.

Reviewer Comment

In all three symptom reduction studies, the graphs that include both failures and completers appear to demonstrate that the treatment effect lasted for at least twelve weeks. As there were few failures in Study 1408, the treatment effects of the "all patients" and "completers" were similar. However, with greater numbers of failures in Studies 1574 and 2233, the treatment effects of the "completers" were not as strongly demonstrated.

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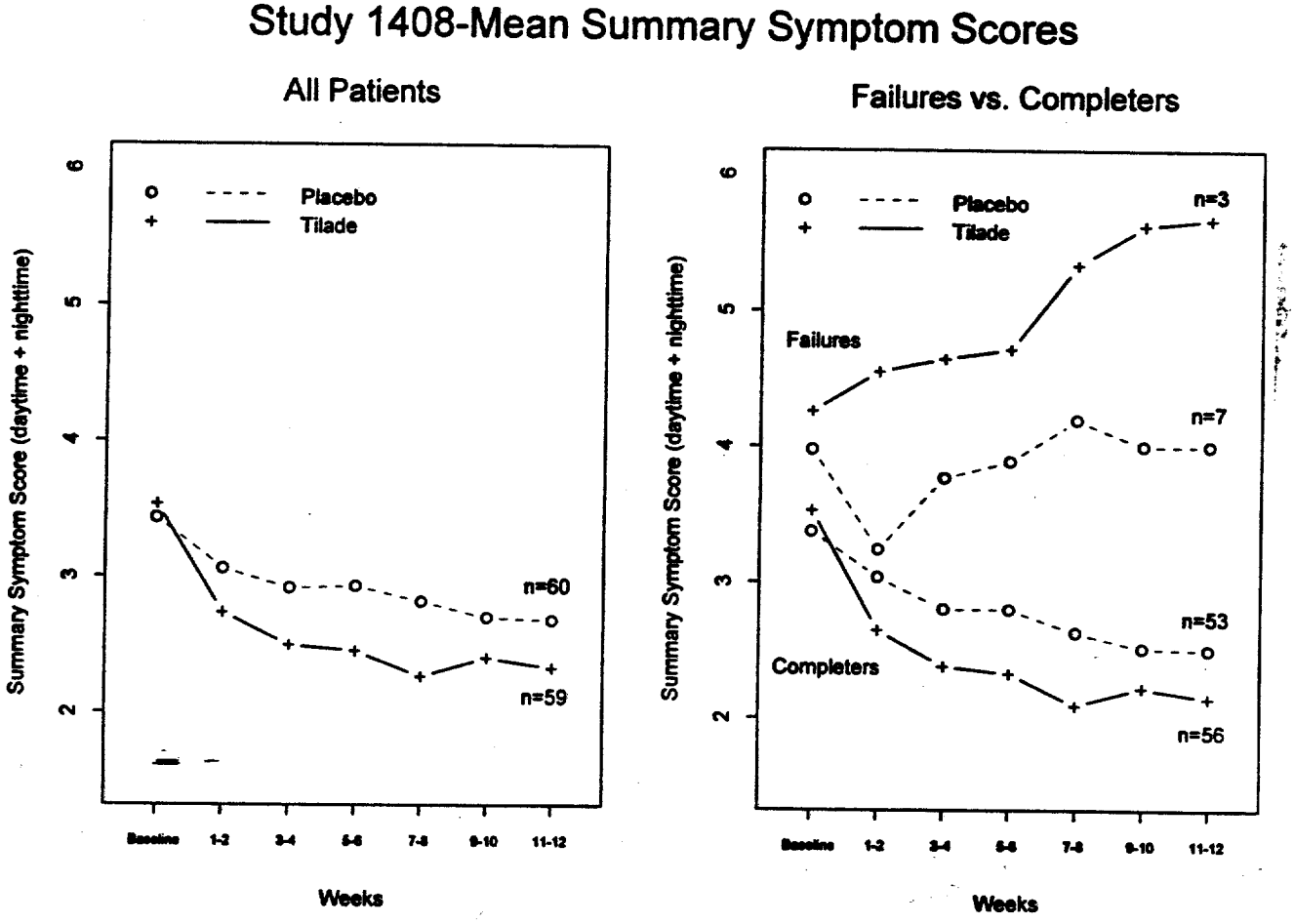

Figure 1: Study 1408 Summary Symptom Score (sum of daytime and nighttime asthma) The patterns of the failures in this study are inconsistent with Studies 1574 and 2333. This discrepancy could be due to the small number of failures in this study.

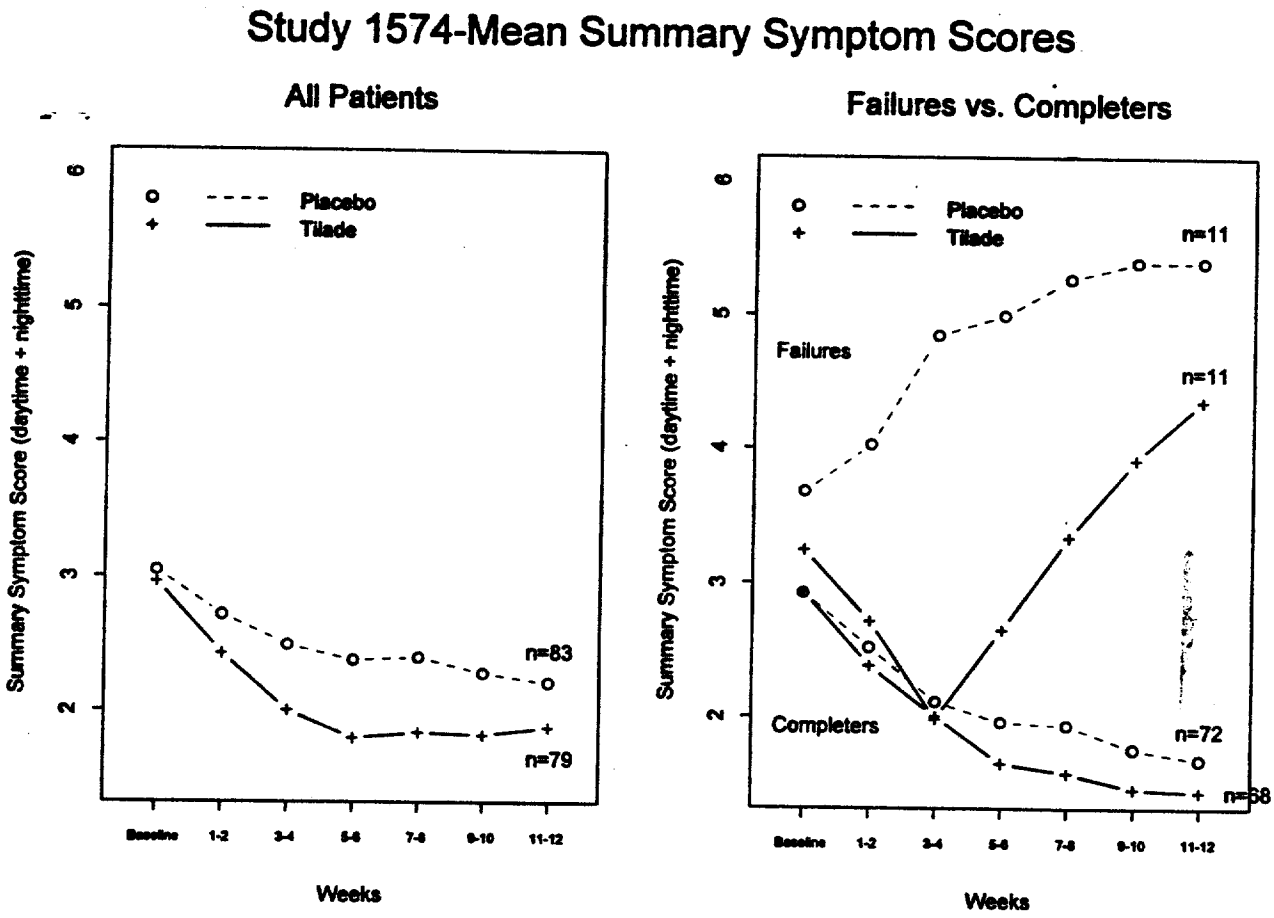

Figure 2: Study 1574 Summary Symptom Score (sum of daytime and nighttime asthma)

Study 2333-Mean Summary Symptom Scores

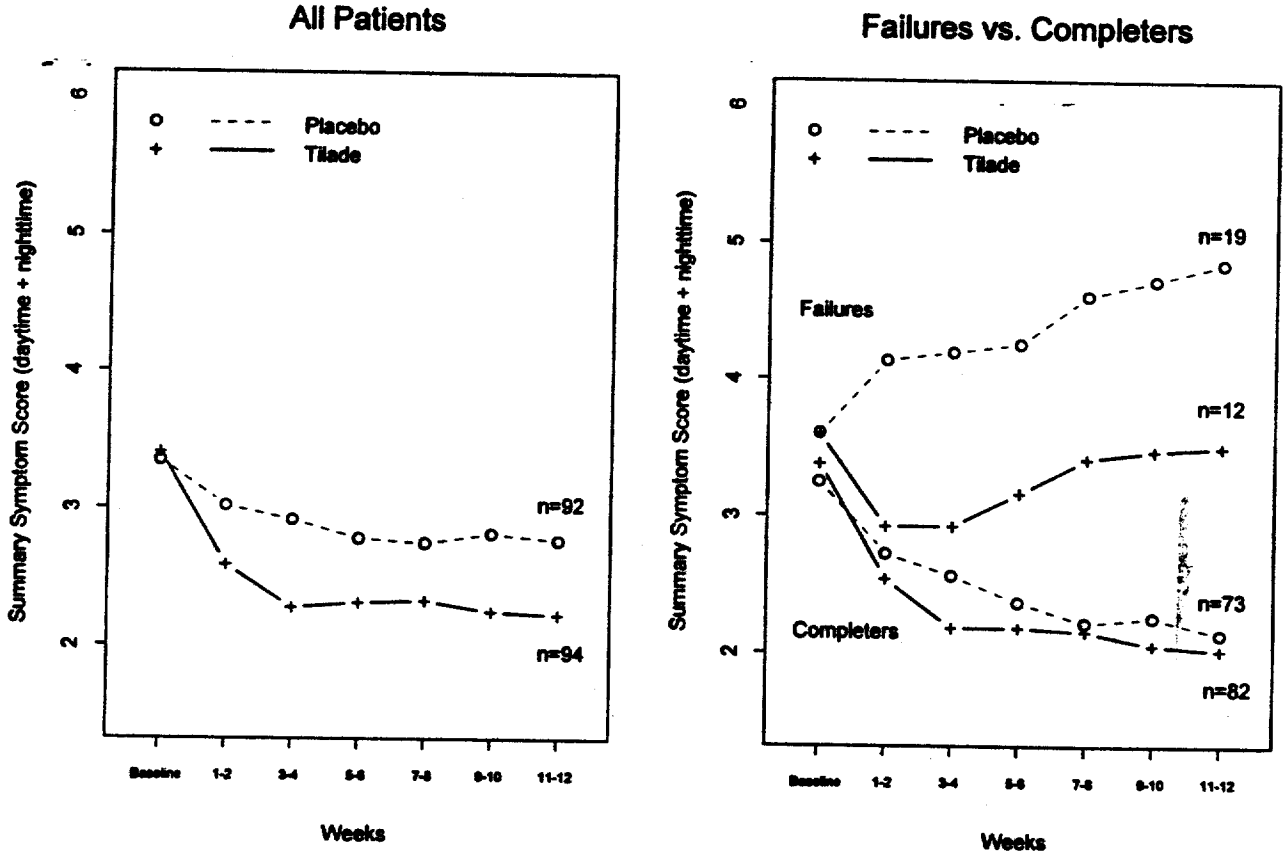

Figure 3: Study 2333 Summary Symptom Score (sum of daytime and nighttime asthma)

2.6.3 Sponsor's Results of Non-Parametric Analyses

The protocols of all five studies specified that the analysis of the primary variable would be "stratified non-parametric analysis of covariance of ranks". A non-parametric, or rank analysis, is an analysis on the *ranks of the variable*, rather than the observed data. Details of the stratified rank analysis follow. For each patient, the change from baseline of each symptom in the symptom complex is calculated. Within each clinic, for each symptom, the scores are ranked according to magnitude of change from baseline. The rank is divided by (n+1) where n is the clinic sample size. For each patient, the ranks of each symptom in the symptom complex is averaged. This average is the dependent variable in the analysis.

The sponsor replaced the stratified rank analysis with the "Conover and Iman" rank analysis *post-hoc*, as the preferred primary analysis. In applying the stratified covariance analysis on the ranks for a variety of other clinical programs, the sponsor has observed "some seemingly irregular patterns". The sponsor reported that,

> "Although a rigorous investigation of the relative efficiency and the finite sample Type I and II error rates of this method with a parametric analysis of covariance or other non-parametric methods...is yet to be conducted, it appears empirically that in a small number of circumstances the stratified rank analysis method does deviate from the cluster of other non-parametric methods in terms of the inferences drawn from each."
>
> Page 8-110-46 of NDA

Therefore, the "more fully studied" approach of analysis of covariance on the rank-transformed data by Conover and Iman was adopted after the protocols of all the studies had been written. (In the Conover and Iman analysis, all the data are ranked together, rather than within each clinic.) The protocol of Study 2333 was amended prior to breaking the blind. Both analyses were performed for all studies (see Table 13). With the exception of Study 1574 (stratified rank analysis: p=0.234; Conover and Iman rank analysis: p=0.025), similar conclusions were drawn from the two different methods. Treatment effect was statistically significant in Studies 1408 and 2233 using both rank analyses. As mentioned, the *post-hoc* rank analysis also yielded statistically significant results for 1574. Additionally, treatment effect in Study 2333 was statistically significant when the *post-hoc* LOCF method was used with the *post-hoc* rank analysis.

Reviewer Comment

In general, Studies 1408 and 2233 were robust to changes in methods of imputation used and populations analyzed (ITT or Efficacy). However, the significance of the treatment effects in Studies 1574 and 2333 depended on the methods used. If the conclusions of the studies were based solely on the results of the protocol-correct analyses, only Studies 1408 and 2233 demonstrated statistical evidence of the efficacy of NSNS.

Table 13: Sponsor's Results using Protocol Specified Primary Time Period / Primary Endpoint / Primary Method of Analysis

Study	Prim. Time Period: Weeks	Primary Endpoint mean of the RANKS of the:		*p*-values: Stratified rank analysis (protocol-corr) WSCF[1]	Stratified rank analysis (protocol-corr) LOCF	Conover & Iman rank analysis (*post-hoc*) WSCF[1]	Conover & Iman rank analysis (*post-hoc*) LOCF
1408	5-12	Δ in the *daytime asthma severity score* & *sleep difficulty score*	ITT	na	0.008[2]	na	na
			Eff	0.008	0.044	na	0.045
1574	3-12[3]	Δ from baseline of worst baseline symptom	ITT	na	na	na	0.008
			Eff	na	0.234	0.060	0.025
2333	3-12	Δ in the *summary score* (daytime + nighttime) & *concomit. med use score*	ITT	na	na	na	0.015[4]
			Eff	0.075	na	0.062	0.016
1978	1-24	Δ in *the daytime asthma severity score* & *sleep difficulty score*	ITT	na	na	na	na
			Eff	0.708[5]	na	0.419	na
				Days w/ Symptoms		Days w/ Symptoms	
2233	1-12	Δ from baseline *% of symptom free days*	ITT	0.017		0.003	
			Eff	0.028		0.006	

1 The protocol correct method of imputing missing values of asthma symptoms was the Worst Score on the scale Carried Forward (WSCF) for Studies 1408, 1574, 2333, and 1978.

2 The table in which this *p*-value was found did not indicate that it was calculated using LOCF, but the introduction to the addendum in which the table was found indicated that, "this addendum focuses on results using the FDA-requested adjustment method for treatment failures." In response to a request by this reviewer (facsimile dated August 12, 1997), the sponsor confirmed that this *p*-value was calculated using LOCF imputed values.

3 The protocol specified the primary time period to be "the final 10 weeks" on page 17 and "the final 8 weeks" on page 24. The study report stated that the primary time period was the final 10 weeks of the double-blind treatment period. The results of the rank analyses for Weeks 5-12 were not submitted. However, using the FDA-requested parametric analysis of covariance, the results were similar on the two different time periods (see Appendix A).

4 In response to a request by this reviewer (facsimile dated August 12, 1997), the sponsor stated that an ITT analysis using LOCF was performed for all variables in Study 2333, but not included in the NDA. The *p*-value in this table ($p = 0.015$) was provided by the sponsor in the facsimile.

5 This *p*-value is based on a *sum* of the ranks of the two symptom scores in the symptom complex, not, as per protocol, the average.

2.6.4 Sponsor's Results of the Parametric Analyses

Table 14 (page 25) presents the results from the sponsor's parametric analysis of covariance on the primary efficacy variable using the primary time period. The first column has the study number and the number of patients, by treatment group, included in the analysis. The means presented in the table are unadjusted means, calculated from the electronic database. For Studies 1408, 2333, and 1574, the data of patients who failed have been imputed after the point of failure using the LOCF method. For Studies 1978 and 2233, the data of patients who failed and those who temporarily failed have been imputed as per the description in section 2.4.3.

The number of patients included in each baseline mean corresponds to the number of patients who were randomized to treatment, less the number of patients who have no baseline data (see Table 8). The number of patients used to calculate each treatment period mean is the number of patients who were randomized to treatment, less the number of patients that withdrew due to reasons other than treatment failure and had data for less than half the treatment period time (see Table 8). The number of patients used to calculate each change from baseline mean is the efficacy population (see Table 8).

The treatment effect is the difference between the two treatments in the means of the primary efficacy variables. It is adjusted for baseline and clinic. The treatment effect was calculated by subtracting the placebo group (adjusted) mean from the NSNS group (adjusted) mean. Thus, for the analyses whereby *reduction* of symptoms was the outcome variable, the sign of the treatment effect was negative when NSNS outperformed placebo. For the analyses whereby an *increase* in percent of symptom free days was the outcome variable, the sign of the treatment effect was positive when NSNS outperformed placebo.

Table 14: Sponsor's *Post-hoc* Parametric Analysis of Covariance Results of Protocol-Specified Primary Time Period & Protocol-Specified Endpoint with Means & Standard deviations calculated from submitted electronic data

Study (Placebo n/ NSNS n)	Primary Efficacy Variable	Population	Period	Placebo Mean ± Std Dev[1]	NSNS Mean ± Std Dev[1]	Treatment effect adjusted for clinic & baseline	*p*-value for treatment effect
1408 (60/60)	Summary Symptom Score	ITT	Baseline	3.44 ± 0.93	3.54 ± 0.91		
			Weeks 5-12	2.80 ± 1.30	2.44 ± 1.30		
			Change from baseline	-0.64 ± 1.16	-1.10 ± 1.26	-0.43	0.037
1574 (83/80)	Worst Baseline Symptom	ITT	Baseline	2.02 ± 0.50	2.06 ± 0.42		
			Weeks 3-12	1.51 ± 0.89	1.21 ± 0.77		
			Change from baseline	-0.51 ± 0.87	-0.85 ± 0.81	-0.32	0.011
2333 (86/89)	Summary Symptom Score	Efficacy[2]	Baseline	3.32 ± 0.76	3.39 ± 0.78		
			Weeks 3-12	2.78 ± 1.45	2.28 ± 1.19		
			Change from baseline	-0.54 ± 1.29	-1.10 ± 1.15	-0.53	0.003
1978 (38/43)	Summary Symptom Score	Efficacy[2]	Baseline	1.29 ± 1.19	1.17 ± 1.05		
			Weeks 1-24	1.09 ± 1.16	0.85 ± 0.80		
			Change from baseline	-0.13 ± 0.98	-0.36 ± 0.97	-0.24	0.1885
2233 (141/138)	Percent Sx-free Days[3]	ITT	Baseline	37.0 ± 31.2	31.6 ± 31.3		
			Weeks 1-12	41.4 ± 30.9	47.9 ± 29.7		
			Change from baseline	+4.2 ± 29.1	+15.9 ± 32.5	8.95 (days)	0.0050

1 The means are unadjusted, and use all patients who had data in the electronic database. The baseline means incorporate more patients than the treatment period and change from baseline means because some patients had data for baseline but not the treatment period (see Table 8).

2 ITT analyses not submitted in NDA. The n reported here is the number of patients that had scores for baseline and at least half of the analysis time period.

3 The protocol specified that a symptom-free day was a day on which the patient had no daytime asthma, nor sleep difficulty due to asthma. No oral steroid was used during symptom free days. The protocol also stipulated that the patients were to use β_2-agonists only if they had symptoms. The sponsor found that a minimal level of prophylactic use was reported (i.e., patients used β_2-agonists on symptom-free days). However, this type of usage was similar in the two treatment groups (mean of 0.21 ± standard error of 0.05 times/day in NSNS group versus 0.20 ± 0.04 in the placebo group, p=0.552). Thus, it did not appear to be an important confounding factor in the comparison of symptom free days between treatments. However, it is likely to have had some effect on the estimate of the treatment effect.

Studies 1408 and 2333 - Symptom Reduction - Adult

Symptom reduction Studies 1408 and 2333 used Summary Symptom Score (daytime and nighttime) as the primary efficacy variable. The treatment effects were statistically significant for both studies (Study 1408: -0.43, p=0.037; Study 2333: -0.53, p=0.003). Recall that the protocol for Study 2333 specified that equal emphasis be placed on the summary symptom score and the concomitant asthma medication score; however, the efficacy of NSNS was to be established based on a single statistical test that combined both variables. (This is the rank analysis presented in Section 2.6.3, Table 13). The parametric analysis does not account for concomitant asthma medication score, thus the results of the summary symptom score endpoint should be examined with the results of the analysis of

Bronchodilator Use. The NSNS patients reduced bronchodilator use (number of times per day, in comparison to baseline) to a greater extent than did the placebo patients (mean treatment difference: -0.11). However, this difference was not statistically significant (p=0.534). It should be noted that in four of the five studies (1408, 2333, 1978, and 2233), the NSNS treatment group decreased the use of the bronchodilator more than did the placebo patients and in Studies 1408 and 2233, this difference approached statistical significance (Study 1408, p=0.061; Study 2233, p=0.095). (See Tables 19 and 20 for additional details.)

Study 1574 - Symptom Reduction - Pediatric

The primary efficacy variable for Study 1574 was the baseline symptom which was most troublesome to the patient during the baseline period. It is referred to as the "worst baseline symptom". Specifically, a patient's worst baseline symptom was defined as follows:

- the symptom with scores of 2 or higher for the greatest number of days during the 2-week baseline period
- if 2 or more symptoms tie on the above criterion, the symptom with the highest average score during the 2-week baseline period
- if 2 or more symptoms tie on the basis of the above criteria, "worst" was defined according to the following ordering: daytime asthma, nighttime asthma and cough.

For the majority of patients, the symptom that was most troublesome during the baseline period was daytime asthma symptom as shown in the table below.

Table 15: "Worst Symptom" during Baseline (% of patients)

	Daytime	Nighttime	Cough
Placebo	70%	6%	24%
NSNS	71%	5%	24%

* Note that the daytime percentages include ties between two or more symptoms. The study report did not indicate how many of these ties occurred.

Statistically significant differences between treatment groups were observed in this study (treatment effect: -0.32, p=0.011). However, inferences from this analysis are compromised by the potentially serious center-by-treatment interaction, (p=0.09). This interaction is examined more closely in Section 2.6.5, pages 27-28. To compare the summary symptom scores (daytime plus nighttime) from Study 1574 with Studies 1408 and 2333, a *post-hoc* analysis was done for this review (see Appendix A). The results were not statistically significant (treatment effect: -0.18, p=0.1329).

Reviewer Comment

In view of the non-significant results of the protocol-defined analysis (see page 23) and the significant center-by-treatment interaction in the post-hoc *analysis, it is difficult to assess the validity of the results from this study.*

Studies 1978 and 2233 - Maintenance - Pediatric

The results from Study 1978 were not statistically significant using the protocol-specified primary efficacy variable (p=0.1885). The cohort of patients in Study 1978 had unusually mild symptoms, with many patients experiencing a number of days with no symptoms. The sponsor hypothesized that with this mild asthmatic population, a more sensitive endpoint would be the percent of symptom free days during baseline compared to the 24-week treatment period. The treatment effect from this endpoint (12.19% difference between treatment groups) was statistically significant in a model with baseline, center and treatment (see Table 16 below). The analysis reported by the sponsor was somewhat problematic and is evaluated in Appendix B.

Table 16: Sponsor's *Post-hoc* Parametric Analysis of Study 1978 using Percent of Symptom-Free Days

Study (Placebo n/ NSNS n)	Primary Efficacy Variable	Population	Period	Placebo Mean ± Std Dev	NSNS Mean ± Std Dev	Treatment effect adjusted for clinic & baseline	p-value for treatment effect
1978 (45/47)	Percent Sx-free Days*	Efficacy	Baseline	42.9 ± 39.8	42.9 ± 39.8		
			Weeks 1-24	46.4 ± 37.3	58.2 ± 33.0		
			Change from baseline	-3.5 ± 27.4	-15.2 ± 35.9	-12.19 days	0.0265

The sponsor designed Study 2233 after the results of Study 1978 showed that summary symptom score was not a sensitive measure in a cohort of mildly asthmatic children. The results of Study 2233 replicated those of the *post-hoc* analysis of Study 1978 see Table 14 above). The treatment effect was statistically significant (8.95, p=0.0050). To compare the summary symptom score results of this study with those of the symptom reduction studies, a *post-hoc* analysis was done for this review (see Appendix A). These results were also statistically significant (treatment effect: -0.36, p=0.0472).

Reviewer Comment

The sponsor's results of the parametric analyses of Studies 1408, 1574, 2333, and 2233 are evidence of the efficacy of NSNS. The conclusions using the parametric analyses differ from those of the stratified rank analyses for Studies 2333 and 1574. The estimated treatment effects ranged from a quarter of a unit to half a unit on a 0-6 scale for Studies 1408, 2333 and 1978.[7] The estimated treatment effect for Study 1574 was about a third of a unit on a 0-4 scale. The treatment effect of Study 2233 is more difficult to interpret because the scale was essentially 0-100. The estimated treatment effect was about nine percentage points on this scale.

2.6.5 Center Effects

Models with center-by-treatment interaction were analyzed to identify any treatment effect differences among the different centers (Table 17). The only study that appeared to demonstrate a potentially serious center-by-treatment interaction was Study 1574, examined below.

[7] The severity of the daytime score was graded on a scale of 0-4 in all studies. The severity of the nighttime scores (sleep difficulty due to asthma and cough) was graded on a scale of 0-2 in Studies 1408, 2333 and 1978, and on a scale of 0-4 for Studies 1574 and 2233.

Table 17: Center-by-Treatment Interactions

Study	Outcome Variable	Model without Center-by-Treatment Interaction (Sponsor's Analyses)			Model with Center-by-Treatment Interaction (Reviewer's Analyses: used efficacy data sponsor submitted)			
		Population	*p*-values		Population	*p*-values		
			Trt Effect	Center Effect		Trt Effect	Center Effect	.Trt*Center interaction
1408	SSS 5-12	ITT	0.037	0.014	Efficacy	0.0537	0.0148	0.9642
2333	SSS 3-12	Efficacy	0.0035	0.0279	Efficacy	0.0171	0.0265	0.6703
1574	WBS 3-12	ITT	0.011	0.013	Efficacy	0.0306	0.0164	0.0915
1978	% Sx-free	Efficacy*	0.0265	0.0233	Efficacy[1]	0.0945[2]	0.0236[2]	0.4395[2]
2233	% Sx-free	ITT	0.0050	0.1160	ITT	0.0028	0.1063	0.2342

1 Only missing 1 patient.

2 The company's analysis combined two of the centers, and yielded different *p*-values (treatment effect was significant, p=0.0248). See discussion in Appendix B.

Study 1574

Table 18 presents results of the individual clinics. NSNS outperformed placebo in five of the seven clinics. The results from Drs. Bronsky and Ginchansky were strongly positive. Dr. Ginchansky's clinic demonstrated the largest treatment effect (-0.94), Dr. Bronsky's center had a more moderate treatment difference (-0.56), and the remaining clinics demonstrated somewhat smaller effects (ranging from -0.23 to -0.48). In contrast, Dr. Dockhorn's and Dr. Ratner's results favored placebo (0.22 and 0.40). If the results of either Dr. Ginchansky's or Dr. Bronsky's center are removed from the analysis, the overall treatment effect is not statistically significant.

Reviewer Comment

This reviewer examined the individual patient data in the two centers that had the largest treatment effects (Drs. Bronsky and Ginchansky). It was apparent that there were no serious outliers in the results of the two centers. Furthermore, though placebo outperformed NSNS in two of the seven centers; one of these two was the smallest center in the study. The significance of the center-by-treatment interaction effect does not appear to seriously devalue the results of this trial.
However, since both the protocol-defined method of analysis and the post-hoc method of analysis encountered problems, the results from this study should be considered "supportive", but not strong evidence of NSNS efficacy.

Table 18: Reviewer's Analysis: (efficacy data only)
Treatment Effects At Each Clinic

Clinic	Placebo N	NSNS N	Treatment Effect	*p*-value
Bronsky	13	11	-0.56	0.0829
Dockhorn	13	12	0.22	0.4882
Ginchansky	12	12	-0.94	0.0039
Kraemer	12	11	-0.48	0.1453
Pearlman	11	10	-0.23	0.5086
Ratner	9	8	0.40	0.2934
Storms	10	12	-0.34	0.3127
Overall Treatment Effect with center-by-treatment interaction in the model	71	76	-0.28	0.0306

2.6.6 Secondary Efficacy Variables

The analyses of the secondary efficacy variables provide supportive evidence of the efficacy of NSNS. The data from Tables 19 and 20 were extracted from tables in the Integrated Summary of Safety and Efficacy. The results are from parametric analyses of covariance.

Table 19: Results of Sponsor's Analyses of Secondary Efficacy Variables: Symptom Reduction Studies

	Study 1408		Study 2333		Study 1574	
Variable	Treatment Difference	*p*-value	Treatment Difference	*p*-value	Treatment Difference	*p*-value
Daytime + Sleep + Cough	-0.90	0.006	-0.84	0.005	-0.75	0.014
Daytime	-0.21	0.095	-0.35	0.012	-0.26	0.045
Sleep Difficulty	-0.26	0.019	-0.21	0.010	-0.17	0.083
Cough	-0.43	0.005	-0.28	0.037	-0.25	0.005
Morning PEFR (l/min)	20.7	0.055	20.7	0.048	13.8	0.032
Evening PEFR (l/min)	9.8	0.309	32.7	0.003	9.9	0.120
Bronchodilator Use (times/day)*	-0.77	0.061	-0.11	0.534	0.2	0.218
FEV_1 (liters)	-0.10	0.122	0.07	0.166	0.05	0.107
FVC (liters)	-0.03	0.619	-0.03	0.866	-0.003	0.548
FEF_{25-75} (l/sec)	-0.12	0.271	0.18	0.037	0.11	0.072
PEFR (l/sec)	0.10	0.676	0.01	0.657	0.14	0.192

Table 20: Results of Sponsor's Analyses of Secondary Efficacy Variables: Maintenance Studies

Variable	Study 1978		Study 2233	
	Treatment Difference	*p*-value	Treatment Difference	*p*-value
Daytime + Sleep + Cough	-0.19	0.323	-0.65	0.014
Daytime	-0.17	0.210	-0.17	0.022
Sleep Difficulty	-0.06	0.356	-0.24	0.060
Cough	0.05	0.455	-0.25	0.011
Morning PEFR (l/min)	15.7	0.157	n/a	n/a
Evening PEFR (l/min)	10.9	0.405	n/a	n/a
Bronchodilator Use (times/day)*	-0.57	0.224	-0.12	0.095
FEV_1 (liters)	0.05	0.105	n/a	n/a
FVC (liters)	-0.01	0.279	n/a	n/a
FEF_{25-75} (l/sec)	0.03	0.317	n/a	n/a
PEFR (l/sec)	-0.05	0.061	n/a	n/a

* Analyses using the electronic data the company submitted were performed for this review for the secondary efficacy variable "Bronchodilator Use". The reviewer was not able to replicate the analyses. The results presented in the table above were labeled "bronchodilator use (times/day)" in the NDA. In the electronic datasets, the units of the variables referred to as "beta-2 agonists" and "albuterol use" were not identified. It was assumed that the variables in the datasets did not measure bronchodilator use in number of times per day. Thus, the results from the sponsor's tables were presented in this review.

PD_{20} post-SRI Episodes

The protocol of Study 1978 defined the primary objective to be "bronchial hyperactivity secondary to respiratory infections...measured by the results (PD_{20}) of a profile of methacholine challenge tests performed three days, three weeks and six weeks after the onset of a documented respiratory infections". However, the primary efficacy variable was defined in the protocol as "the symptom complex of daytime asthma severity and sleep difficulty due to asthma" over the entire treatment period, weeks 1-24. Therefore the study was designed to detect a statistically significant difference in reduction of symptom scores, regardless of upper respiratory infections, not an increase in PD_{20} post-symptomatic respiratory infections (SRI). The study report reiterated these definitions. However, the integrated summary of efficacy stated that the primary efficacy variable was PD_{20} post-SRI episodes. Therefore, the results of the PD_{20} analyses are presented here.

The sponsor predicted that more than one episode of SRI may have occurred in some patients. Thus, the protocol stated that two analyses would be performed, one on the SRI with the lowest PD_{20} and another on the average PD_{20} across all SRIs. Only the results of the latter analysis were submitted. The sponsor expected that,

> "a difference between treatments would likely be demonstrated by differences at either three weeks or six weeks post-SRI. That is, once an SRI occurs, bronchial hyperreactivity will increase. Patients receiving the active drug may have a shorter duration of increase in bronchial hyperreactivity and, hence, higher PD_{20} at three weeks and six weeks post-SRI."
>
> Protocol, Page 8-66-37 of NDA

The results of the study demonstrate that there were slight increases in PD_{20} among the NSNS patients at "onset of SRI", 3 weeks and 6 weeks post-SRI. However, the mean differences in PD_{20} at 3 and 6 weeks post-SRI were not statistically significant (3 weeks, p=0.820; 6 weeks, p=0.808). Additionally the mean difference in PD_{20} between treatment groups at "onset of SRI", an endpoint that the sponsor did not expect to find statistically significant, approached statistical significance (reported as p=0.051 on pages 8-60-21 and 8-110-103 of NDA; and as p=0.053 on pages 8-60-20 and 8-110-77 of NDA).

In addition to analyzing PD_{20} after SRI episodes, asthma symptoms of patients were analyzed during SRI episodes. Study 2233 was designed similarly. To evaluate the effect of NSNS on patients' symptoms during SRI episodes, the protocols stated that a summary asthma symptom score during the 14-day period after the start of oral steroids was to be examined. All the asthma symptoms during the 14-day periods were similar across treatment groups in both studies. However, descriptive statistics of the percent of patients with SRIs and percent of patients with SRIs who needed prednisone interventions demonstrated differences between the two treatment groups in Study 2233. These differences are presented in detail in Appendix C.

Reviewer Comment
The methacholine challenge test (PD_{20}) did not appear to be a sensitive measure of the difference between the two treatment groups during or after an SRI episode. It is not clear whether this was a consequence of the fact that the study was not powered to detect a difference, or whether there was no true difference.

3. Conclusions

The company submitted eight placebo controlled studies to support the efficacy of Tilade Nebulizer Solution. This reviewer concluded that the statistical results from Studies 1408 (adult), 2333 (adult) and 2233 (pediatric) provide evidence of the efficacy of Tilade Nebulizer Solution.

Four adult studies (1408, 2333, 1409, and 1691) and one pediatric study (1574) were identified as "symptom reduction studies". These studies were designed to show a reduction in asthma symptoms among patients with moderate levels of asthma symptoms, in terms of both severity and frequency. Studies 1408 and 2333 provide evidence of the efficacy of Tilade Nebulizer Solution. A *post-hoc* analysis of Study 1574 provides *supportive* evidence of the efficacy of Tilade Nebulizer Solution in adults with asthma. As noted in the review, inferences from Study 1574 are compromised by the observed interaction between treatment and center.

Four additional pediatric studies (1978, 2233, and 3003) were identified as "maintenance studies". These trials studied the clinical benefits of Tilade Nebulizer Solution in children with mild, episodic symptoms. Based on this reviewer's evaluation, Study 2233 provides evidence that Tilade Nebulizer Solution is efficacious in patients ages 2-5. Study

1978 was informative in that the positive results from *post-hoc* analyses were replicated by Study 2233.

Barbara Bono 9/22/97

Barbara Bono
Mathematical Statistician

concur: Dr. Wilson JEW 9/22/97
Dr. Nevius SEN 9/22/97

cc:
Orig. NDA 20-750
HFD-570 / Division File
HFD-570 / JJenkins, RMeyer, BOtulana
HFD-715 / Chron
HFD-715/ BBono, SWilson, ENevius

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APPENDIX A

The analyses presented in this appendix were performed by this reviewer to supplement and assist in the comprehensive review of the results of the studies. They are referenced in the body of the review as *supportive* evidence of the efficacy of NSNS.

Table A.1
(Summary Symptom Score: sum of daytime and nighttime asthma)

Study Placebo n / NSNS n	Primary Efficacy Variable	Population	Time Period	Placebo Mean ± Std Dev	NSNS Mean ± Std Dev	Treatment effect adjusted for inv & bsl	*p*-value for treatment effect
1408 46/47	Summary Symptom Score	without Steinberg's clinic	Baseline	3.34 ± 0.91	3.49 ± 0.91		
			Weeks 5-12	2.77 ± 1.29	2.38 ± 1.35		
			Change from baseline	-0.60 ± 1.22	-1.14 ± 1.29	-0.48	0.0499
1978 45/47	Percent Sx-free Days	Efficacy	Baseline	42.9 ± 39.8	42.9 ± 39.8		
			Weeks 1-24	46.4 ± 37.3	58.2 ± 33.0		
			Change from baseline	-3.5 ± 27.4	-15.2 ± 35.9	-12.19	0.0265
1574 79/76	Worst Baseline Symptom	Efficacy	Baseline	2.05 ± 0.52	2.06 ± 0.43		
			Weeks 5-12	1.48 ± 0.94	1.17 ± 0.86		
			Change from baseline	-0.55 ± 0.91	-0.87 ± 0.89	-0.30	0.0293
1574 80/76	Summary Symptom Score	Efficacy	Baseline	3.05 ± 1.10	2.97 ± 1.10		
			Weeks 3-12	0.89 ± 0.91	0.68 ± 0.71		
			Change from baseline	-2.15 ± 1.07	-2.26 ± 0.99	-0.18	0.1329
1574 79/76	Summary Symptom Score	Efficacy	Baseline	3.05 ± 1.1	2.96 ± 1.10		
			Weeks 5-12	0.88 ± 0.95	0.68 ± 0.79		
			Change from baseline	-2.16 ± 1.10	-2.25 ± 1.04	-0.16	0.2044
2233 136/134	Summary Symptom Score	Efficacy	Baseline	2.86 ± 1.88	3.14 ± 1.93		
			Weeks 1-12	2.79 ± 1.93	2.44 ± 1.59		
			Change from baseline	-0.15 ± 1.93	-0.69 ± 1.90	-0.36	0.0472

APPENDIX B

Study 1978

The primary efficacy variable in Study 1978 was Summary Symptom Score. However, the results of Study 1978, based on this variable, were not statistically significant. In an addendum to the study report, the sponsor proposed that in this study population of mild to moderate asthmatics, maintenance of symptom free time was a relevant measure of the efficacy of an asthma therapy. From a statistical standpoint, the analysis of the study had two problems. In the post-hoc analysis,

1. the sponsor did not follow the protocol in assessing center-by-treatment interaction, and
2. the sponsor combined two of the centers, influencing the statistical results from the trial.

For the original analysis, the protocol stated that a stepwise procedure would be used to arrive at the final model.

> "The procedure involves the examination of the results based on preliminary models and the progression to reduced models if interactions are not significant ($p<0.05$)."
>
> p. 33 of protocol, p. 8-66-39 of NDA

This procedure was followed for the primary efficacy variable analyses in the study report. However, in the addendum to the study report where the variable Percent of Symptom Free Days was first introduced, the sponsor's final model included the center-by-treatment interaction, even though the interaction was not significant.

In addition, the sponsor's model combined the two smallest centers into one center in the analysis. The practice of combining centers puts less weight on each individual center in the combination. The sponsor's analysis put less weight on each of the two negative centers than on the positive centers. More appropriate analyses would either, 1) weight all centers equally ("equal weights " - a procedure often proposed for cases with center-by-treatment interaction)[8], or 2) weight all centers according to the size of the center ("harmonic weights). The results of these three analyses are presented in Table B.1.

[8] In SAS, this is known as "Type III Sums of Squares".

Table B.1: Reviewer's Analysis: (efficacy data only)
***Post-hoc* variable: Percent of Symptom Free Days**
Treatment Effects At Each Clinic

Clinic		Placebo N	NSNS N	Trt Effect	*p*-value
1	E. Ellis	4	4	-15.6	0.3708
2	Eigen	5	4	- 3.4	0.8542
3	Geller	8	9	5.8	0.6441
4	Konig	8	9	20.8	0.1021
5	M. Ellis	8	9	21.0	0.0983
6	Shapiro	7	6	28.9	0.0478
7	Welch	5	6	9.2	0.5567
Overall Treatment Effect with center-by-treatment interaction in the model	1. centers 1& 2 combined	45	47	12.5	0.0248
	2. harmonic weights			12.2*	0.0268
	3. equal weights			9.5	0.0945

* There was no option available in SAS 6.12 to calculate the treatment effect using SAS Type II Sums of Squares (harmonic weights), thus this treatment effect was obtained using Cross-Graphs.

The treatment effects for each center, using each of the different types of weighting methods, are presented graphically with the overall treatment effects in Figure B.1.

Reviewer Comment
The center-by-treatment interaction effect was not statistically significant, thus a model without the center-by-treatment interaction could be argued to be most appropriate model from which to draw inference. The treatment effect, using this parametric analysis of covariance model, was significant (see Table 17).

In light of these observations, additional analyses to test the results of the different weighting schemes were also performed for Study 2233. These results are discussed below.

Figure B.1: Study 1978

Treatment Effects by Center (numbered) &
Overall Treatment Effects Harmonic Weights: weights centers by size
Equal Weights: weights all centers equally

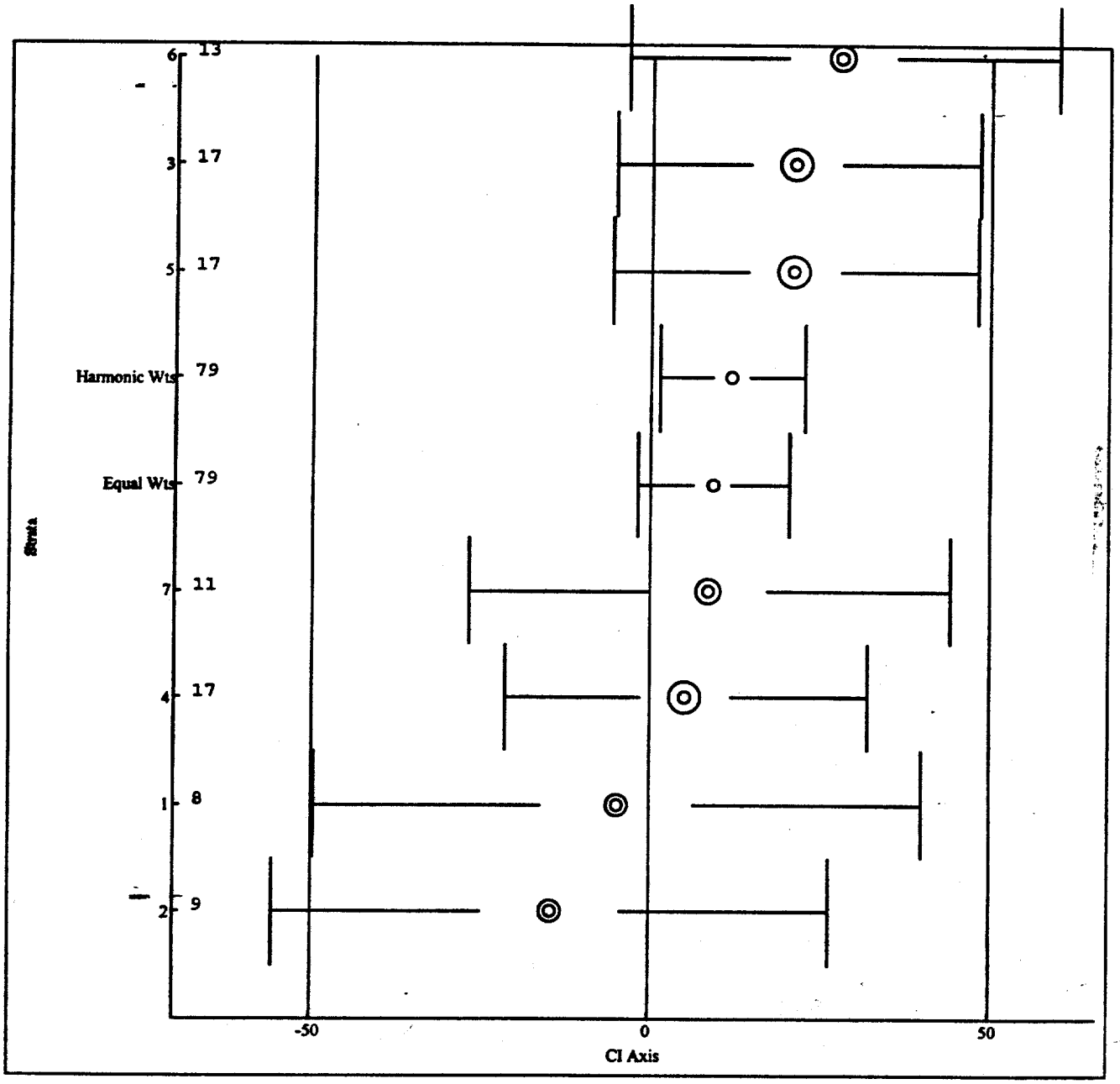

Figure B.1: Numbers to the left of the y axis indicate the clinic number (identifiable by investigator's name in Table B.1. Numbers to the right of the clinic number indicate the total sample size in each clinic. The size of the circle represents the size of the clinic.

Study 2233

Study 2233 was a 12-week study in a group of 279 mildly asthmatic children ages 2-5, with Percent of Symptom Free Days as the primary efficacy variable. Since this study was designed based on Study 1978, it is worthwhile to compare the individual center results of this study with those of Study 1978. Twelve of the 15 centers in the study found a positive treatment effect (see Table B.2 below). The centers were somewhat unbalanced in size, but the treatment effect was statistically significant using either of the two weighting methods described above.

Table B.2: Reviewer's Analysis: (efficacy data only)
Treatment Effects At Each Clinic

Clinic		Placebo N	NSNS N	Trt Effect	*p*-value
1	Bell	4	4	19.7	0.2802
2	Bronsky	11	9	14.4	0.2162
3	Bukstein	7	9	18.9	0.1468
4	Ellis	7	7	21.1	0.1280
5	Geller	9	9	-2.9	0.8121
6	Klimas	10	10	-14.0	0.2274
7	Kraemer	11	11	11.5	0.2980
8	Lemen	8	8	7.5	0.5590
9	Mellon	10	10	5.6	0.6264
10	Pearlman	10	9	6.6	0.5773
11	Smith	15	13	14.8	0.1333
12	Szefler	10	9	35.3	0.0031
13	Thomas	11	11	-15.8	0.1534
14	Welch	8	8	14.9	0.2484
15	Wood	8	7	9.7	0.4720
Overall Treatment Effect with center-by-treatment interaction in the model	harmonic weights	139	134	8.9*	0.0054
	equal weights			9.8	0.0028

* There was no option available in SAS 6.12 to calculate the treatment effect using SAS Type II Sums of Squares (harmonic weights), thus this treatment effect was obtained using Cross-Graphs.

The treatment effects for each center are presented graphically (see Figure B.2) along with the overall treatment effects using each of the different types of weighting methods.

Figure B.2: Study 2233

Treatment Effects by Center (numbered) &
Overall Treatment Effects Harmonic Weights: weights center by size
Equal Weights: weights all centers equally

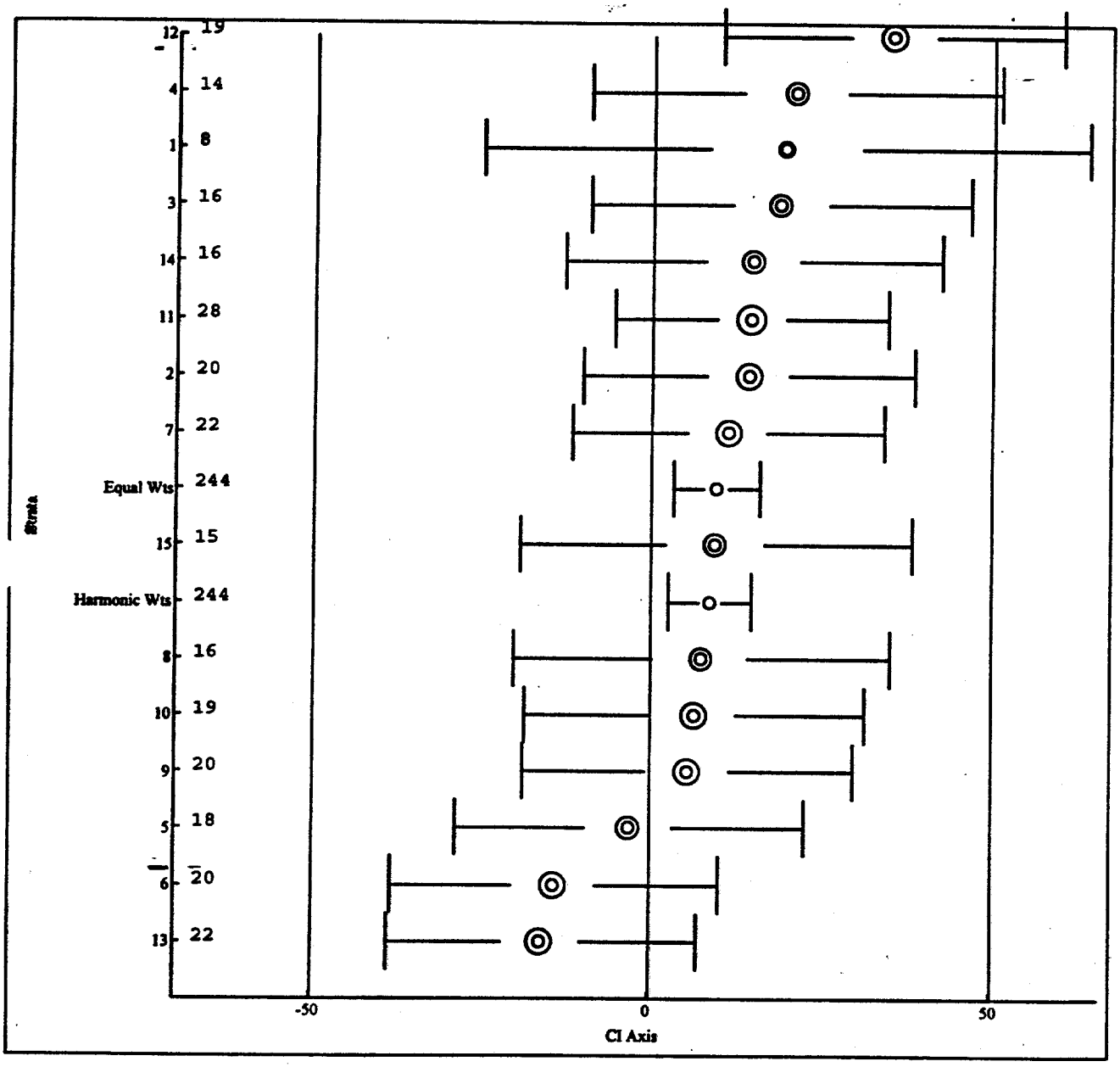

Figure B.2: Numbers to the left of the y axis indicate the clinic number (identifiable by investigator's name in Table 20). Numbers to the right of the clinic number indicate the total sample size in each clinic. The size of the circle represents the size of the clinic.

Appendix C

Upper Respiratory Infections

To evaluate the effect of NSNS on patients' asthma symptoms during a symptomatic or upper respiratory infection (URI) episode, the protocols for 1978 and 2233 stated that a summary asthma symptom score during the 14-day period after the start of oral steroids was to be examined. All the asthma symptoms during the 14-day periods were similar across treatment groups in both studies. However, descriptive statistics of the percent of patients with URIs and percent of patients with URIs who needed prednisone interventions demonstrated differences between the two treatment groups in Study 2233.

In Study 2233, one or more episodes of clinically confirmed URI were seen in 71% of the NSNS patients and 77% of the placebo patients. Multiple episodes during the 12-week treatment period were common in both groups. Among those patients who had clinically confirmed episodes of URI, 36.5% of patients in the placebo group required prednisone intervention while 29.5% of patients in the NSNS group did. Two *post-hoc* analyses done for this review found marginally statistically significant results for the endpoint "number of patients with prednisone interventions" for Study 2233. The first analysis compared the percent of patients who had at least one prednisone intervention in the placebo group with that in the NSNS group using the chi-square test (Table C.1, p=0.091). A more powerful test for this type of data is the trend test comparing the percent of patients in the two treatment groups requiring one, two, three, four or five prednisone interventions (Table C.2, p=0.0560). These data are displayed graphically in Figures C.1-C.2.

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Table C.1: Descriptive Statistics of URIs*

	1978			2233		
	NSNS n=48	Placebo n=45	*p*-value	NSNS n=132	Placebo n=137	*p*-value
Number (%) of patients with clinically confirmed URI	33 (68.8%)	31 (68.9%)	0.989	93 (70.5%)	105 (76.6%)	0.250
Number (%) of patients with prednisone interventions associated with URI	Not Available	Not Available	Not Available	39 (29.5%)	50 (36.5%)	0.226
Number of patients with prednisone use unrelated to URI	Not Available	Not Available	Not applicable	1	5	Not applicable
Total number (%) of patients with prednisone interventions	15 (31.3%)	17 (37.8%)	0.508	40 (30.3%)	55 (40.1%)	0.091
Number of courses of prednisone	25	32	Not applicable	57	82	Not applicable
Total number of days of prednisone therapy per patient (mean ± S.E)	12.1 ± 2.2	12.9 ± 2.1	Not applicable	9.65 ± 0.80	10.16 ± 0.77	Not applicable

* *P*-values obtained using a chi-square test.

* Study 1978 referred to the infections as "symptomatic respiratory infections (SRIs)". Study 2233 referred to the infections as "upper respiratory infections (URIs)".

Table C.2: Study 2233 Trend Test Number of Patients with Clinically Confirmed URI Episodes

	Number of Patients with Clinically Confirmed URI Episodes (URIs)								
	0 URIs	1 URI	2 URIs	3 URIs	4 URIs	5 URIs	6 URIs	Total	*p*-value
Placebo	32	38	41	21	4	0	1	137	
NSNS	39	34	30	21	8	0	0	132	0.3656

Table C.3: Study 2233 Trend Test Number of Patients with Prednisone Interventions

	Number Patients with Predinisone Interventions (PIs)							
	0 PIs	1 PI	2 PIs	3 PIs	4 PIs	5 PIs	Total	*p*-value
Placebo	82	35	16	2	1	1	137	
NSNS	92	25	13	2	0	0	132	0.0560

* *P*-values obtained using a trend test.

Figure C.1

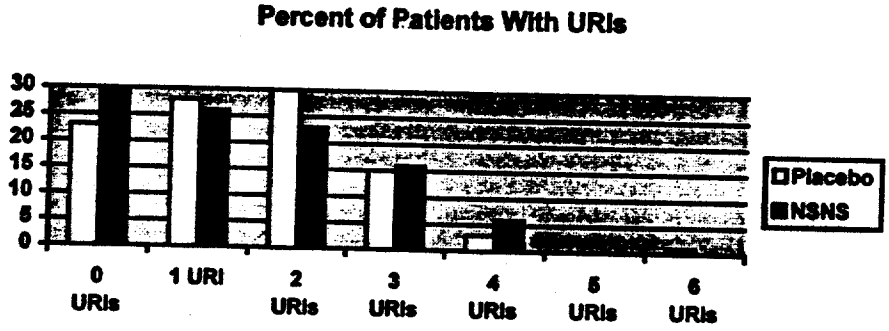
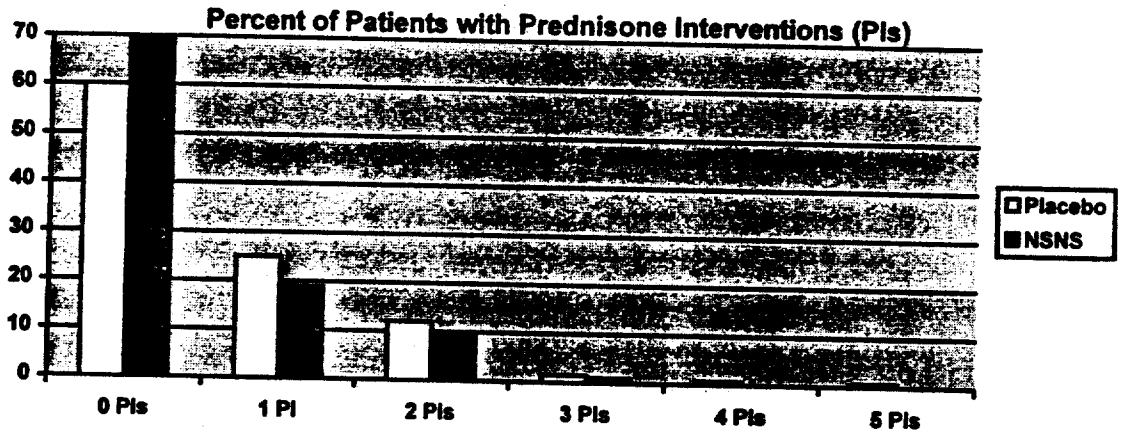


Figure C.2



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20750

MICROBIOLOGY REVIEW(S)

JUN 13 1997

REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 20-750
9 June 1997

A. 1. NDA 20-750

APPLICANT: Fisons Pharmaceuticals
Fisons Corporation
Rochester, NY 14623

2. PRODUCT NAMES: Tilade® Nebulizer Solution (nedocromil sodium inhalation solution)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile solution for inhalation.

4. METHODS OF STERILIZATION:
The drug product is

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated in the treatment of mild to moderate asthma.

B. 1. DATE OF INITIAL SUBMISSION: 30 September 1996

2. DATE OF AMENDMENT: 12 May 1997 (subject of this review)

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: 28 May 1997

C. REMARKS:

Fisons Corporation is a subsidiary of:

Rhone-Poulenc-Rorer Pharmaceuticals, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

D. CONCLUSIONS: The application is recommended for approval on the basis of sterility assurance.

The applicant should be reminded of their commitment

7 June 1997

Paul Stinavage, Ph.D.

PAC 6/13/97

cc: Original NDA 20-750
HFD-570/B. Gallauresi
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 9 June 1997
R/D initialed by P. Cooney

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REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 20-750
8 January 1997

A. 1. NDA 20-750
APPLICANT: Fisons Pharmaceuticals
Fisons Corporation
Rochester, NY 14623

2. PRODUCT NAMES: Tilade® Nebulizer Solution (nedocromil sodium inhalation solution)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile solution for inhalation.

4. METHODS OF STERILIZATION:
The drug product is

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated in the treatment of mild to moderate asthma.

B. 1. DATE OF INITIAL SUBMISSION: 30 September 1996

2. DATE OF AMENDMENT:

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: 23 October 1996

C. REMARKS:
Fisons Corporation is a subsidiary of:

Rhone-Poulenc-Rorer Pharmaceuticals, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns.

7 January 1997
Paul Stinavage, Ph.D.

cc: Original NDA 20-750
HFD-570/B. Gallauresi
HFD-805/Consult File/Stinavage

Date 1/8/97

Drafted by: P. Stinavage, 7 January 1997
R/D initialed by P. Cooney

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