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APPLICATION NUMBER: NDA 20750

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-750	APPLICATION TYPE:	NDA
SPONSOR:	Rhone-Poulenc Rorer	PRODUCT/PROPRIETARY NAME:	Tilade
		USAN / Established Name:	Nedocromil
CATEGORY OF DRUG:	Anti-inflammatory	ROUTE OF ADMINISTRATION:	Inhalation Solution
MEDICAL REVIEWER:	B. A. Otulana, MD	REVIEW DATE:	Sept 12, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
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RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
Oct 29, 1987	IND	IND under which studies were done

Overview of Application/Review:

This is an original NDA for Tilade Nebulizer Solution. The efficacy and safety are supported by 8 pivotal US studies, 6 additional non-US controlled trials and 2 US open-label, long-term safety trial, all in asthma. The studies covered the age range 2-70 years for which the drug will be indicated. The studies addressed the use of Tilade for symptom reduction and for maintenance therapy. Overall, about half of the studies were positive for efficacy, but they all supported the safety of Tilade in patients with mild to moderate asthma.

Outstanding Issues:

Recommended Regulatory Action: | **N drive location:**

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: __X__ Approvable _____ Not Approvable

Signed: **Medical Reviewer:** _____ **Date:** 9/22/97

Medical Team Leader: _____ **Date:** 9/22/97

cc:
NDA 20-750
HFD-570
Division file
Otulana, Meyer, Bono, Gallauresi, Chen, Kim, Vogel

00 RÉSUMÉ

01 PIVOTAL STUDIES REVIEWED

Study	Dosing Regimen	Duration	No. of patients	Age range
SYMPTOM REDUCTION STUDIES				
CR1408	QID	12 Weeks	123	13-70
CR2333	QID	12 Weeks	189	12-81
CR1574	QID	12 Weeks	166	6-12
CR1409	QID	12 Weeks	121	12-70
CR1691	TID	12 Weeks	139	12-67
MAINTENANCE STUDIES				
CR1978	TID	24 Weeks	93	6-12
CR2233	TID	12 Weeks	279	2-5
CR3003	TID	12 Weeks	293	5-12

02 OVERALL EFFICACY

This application was supported by a number of US and non-US trials. The sponsor designated 8 US studies shown in the table above as the pivotal trials. As tabulated above, the studies were divided into two categories: symptom reduction trials and maintenance trials. The goal of the Tilade Nebulizer Solution program was to demonstrate that the drug could provide benefit in asthmatic patients who already had on-going symptoms by reducing their symptomatology, as well as in symptom-free patients who require therapy to prevent development of asthmatic symptoms. The studies included children aged 2 years and above, adolescents, and adults up to age 70 years.

Five studies, as shown in the table above, were classified as 'symptom reduction' studies. Studies CR1408, CR2333, CR1409 and CR1691 were the symptom-reduction trials carried out in adults. These studies were all 12-weeks in duration, and were double-blind, placebo-controlled enrolling mild to moderate asthmatics. Their design was similar: a 2-week run-in, 2-week baseline, and 12-week treatment period. The dose of the drug given in all the studies was 1 ampule (11 mg) four times daily except in study CR1691 where the drug was given three times daily. In general, the main efficacy endpoint was some combination of the various symptom scores recorded in patient's daily diaries into a composite score. The individual symptoms scored during the study included daytime asthma, sleep difficulty and cough. Concomitant medication was also scored. In study CR1408, CR1409 and CR1691, the summary symptom score was the primary efficacy variable. In study CR2333, the summary symptom score was combined with the concomitant medication use for the primary efficacy variable. In all studies, the sponsor chose the last 8

weeks (studies CR1408, 1409 and 1691) or last 10 weeks (in CR2333) as the primary efficacy time period. The reason for this choice was to ensure that the analysis captured the period when Tilade would be expected to be active, since onset of action could be up to 2 weeks or longer. Individual asthma symptoms were treated as secondary efficacy variables along with morning and evening PEFR recorded by the patients, spirometry measurements at each clinic visits, and physician and patient rating of effectiveness at the end of the study. In all cases, compliance was only monitored by checking the patient's diary recording of drug use.

The four symptom-reduction studies in adults were not uniformly successful. In CR1408, Tilade beat placebo with statistically significant difference ($p=0.034$) on the primary efficacy variable as well as on some of the secondary efficacy endpoints such as daytime asthma and cough. However, no statistically significant superiority was established on the more objective endpoints such as AM and PM PEFR, and FEV_1 nor on concomitant medication use although the trends on these variables were in the right direction. In study CR2333, Tilade showed numerical advantage over placebo but failed to achieve statistical significance on the summary symptom score/concomitant medication use endpoint averaged over weeks 3-12 ($p=0.06$). When assessed over the entire 12-week period though, Tilade was significantly better than placebo, and it also beat placebo on sleep difficulty, AM PEFR and FEV_1. Both studies CR1409 and CR1691 failed to show efficacy for Tilade on the primary efficacy variable as well as on most of the secondary efficacy endpoints. They therefore did not contribute to establishing the efficacy of this drug in symptomatic adult asthmatics.

Study CR1574 was the only study done to support symptom reduction claim for Tilade in children. Patients who were aged 6-12 years were followed up for 12 weeks on Tilade or placebo given at 1 ampule four times daily. The general design was similar to the adult studies described above. However a new endpoint, the 'worst symptom' was used as the primary variable. This was defined as the most troublesome symptom recorded by the patient during the baseline period. For over 70% of the patients, this symptom was the 'daytime asthma', while it was 'cough' in 24% of the patient. Tilade demonstrated a statistically significant efficacy over placebo on the 'worst symptom' variable, as well as on the individual symptom scores. Tilade also beat placebo on AM PEFR but not on nighttime asthma, bronchodilator use or FEV_1.

It should be pointed out that in the mild to moderate asthmatics enrolled in the studies discussed above, the size of the difference between Tilade and placebo, and indeed the change from baseline in the efficacy variables were usually very modest even where statistically significant changes were found. Thus in study CR2333 for instance, although the 'worst symptom' improved from 2.06 to 1.20 (on a 0-4 scale) in the Tilade group, the placebo patients also improved from 2.02 to 1.51, making the mean difference between active drug and placebo a mere 0.32 on a 5-point scale.

The maintenance studies were all in children. The objective in this category of studies was to show that Tilade could maintain patients with mild asthma symptom-free during the treatment period. There were three studies under this classification. The overall design was similar to the symptom-reduction study in terms of diary recordings of symptoms, clinic visits, variables recorded etc. but the patient population and efficacy endpoints differed from those in the symptom-reduction studies. The first study carried out, CR1978, was of 24-week duration. The other two, studies CR2233 and CR3003 were of 12-week duration. The main efficacy endpoint in study CR1978 was summary symptom score but the percentage of symptom-free days was also analyzed *post-hoc*. For studies CR2233 and CR3003, the percentage of symptom-free days was the protocol-defined primary endpoint.

Study CR1978 was a small study (n=93) in children aged 6 to 12 years who had very mild asthma at onset, with nearly 43% symptom-free days during the 2-week baseline period. During the 24-weeks treatment period, Tilade failed to beat placebo on the primary efficacy variable: the summary symptom score (which consisted of daytime asthma scores plus sleep difficulty scores). Tilade also did not beat placebo on the secondary endpoints: the individual symptom scores (daytime asthma, sleep difficult and cough severity) or on morning and evening PEFR and concomitant medication. However, on a *post-hoc* analysis of the percentage of symptom-free days over the 24 week treatment period, Tilade was significantly superior to placebo by increasing the percentage of symptom-free days from about a mean 43% at baseline to 58% mean at the end of the 24-week period. The placebo group only changed from a mean 43% to 46% over the same period. The difference was significant at p=0.025. The sponsor argued that this *post-hoc* analysis was appropriate for the design of the study and the patient population (very mild asthma) enrolled.

Study CR2233 was larger than CR1978 (n=279) but followed as similar design except that the patients were 2 to 5 years old and the primary variable, the percent symptom-free days, was pre-specified. Tilade showed a statistically significant superiority over placebo on this endpoint Tilade also beat placebo on some of the other efficacy endpoints such as summary symptom score, daytime asthma and cough. However, Tilade did not beat placebo on the semi-objective secondary efficacy variable, the child's activity level, assessed by the parent or guardian on a visual analogue scale. Finally, study CR3003, the largest of the 'maintenance' studies, was carried out on a similar protocol in patients aged 5 to 12 years. In this trial, Tilade demonstrated a numerical advantage over placebo on the primary endpoint, the percentage of symptom-free days, as well as on additional endpoints, daytime asthma, sleep difficulty, cough and morning peak flow rate. However, the differences between Tilade and placebo did not achieve statistical significance on any of these comparisons.

Overall, the efficacy of Tilade was spotty in the two programs: symptom-reduction trials and maintenance trials. As discussed above, some studies were positive, most were marginal and about half of the US pivotal studies were negative, on efficacy analysis. Nonetheless, studies CR1408 provide positive data in the use of Tilade in adult asthmatics with symptoms. It is somewhat supported by study CR2333, where Tilade came close to beating placebo, with a p value of 0.06. For symptom reduction in children, study CR1574 with data in asthmatics aged 6 to 12 years did provide evidence in support of the efficacy of Tilade over placebo. In the category of maintenance studies where all the studies enrolled children, study CR2333 in asthmatics aged 2 to 5 years was conclusively positive in favor of Tilade. And study CR1978 in the older children (aged 6-12) provided some support based on the favorable *post-hoc* demonstration of efficacy. Although not all studies were positive, there were sufficient data to support the efficacy of Tilade for the claimed indication (maintenance therapy) and in the asthmatic population proposed in the labeling (aged 2 years and older)

03 OVERALL SAFETY

The safety database of Tilade consisted mainly of the data from the 14 placebo-controlled US and non-US studies as well as the two US open-label 52-week studies. A total of 1076 patients received Tilade in these studies while 933 received placebo. The safety profile, as discussed in the integrated safety summary (ISS), conformed with the excellent safety usually associated with the nedocromil drug substance. The most outstanding adverse event (AE) was taste perversion (or unpleasant taste), with overall occurrence at a 4:1 proportion when Tilade is compared to placebo. The usual respiratory system events associated with most asthma drugs such as URI, coughing, bronchospasm, dyspnea etc. occurred in a substantial

proportion of the study patients but at nearly equal frequency on Tilade and placebo. In a few of the individual pivotal studies, some adverse events showed greater frequency on the active drug compared to placebo. These included headache, chest pain, bronchitis and other airway-related events. However, these trends were not seen when the controlled trials were pooled for the integrated safety summary.

There were no major gender differences in the reported adverse events except that taste perversion was more frequently reported by males (5:1 active:placebo ratio) than females (4:2 active:placebo ratio). Slight gender trends were also seen on gastroenteritis (3:1 male:female ratio) and diarrhea (1:3 male:female ratio). There were also no clear-cut age differences in the reporting of adverse events in the pivotal database. The 6 to 11 year old appeared to report more incidences of fever, chest pain and abdominal pain but the clinical significance of this finding is doubtful.

There was only one death in the study, perhaps reflecting the preponderance of children in the database and the mildness of asthma in the patients enrolled. The dead was a 48-year old Tilade-treated female patient in a non-US trial. She was said to have died from myocardial infarction.

Twelve percent of the patients who received Tilade in the controlled trials (total n=936) dropped out of the study, compared to 13.3% on placebo (total n=933). About 6% on each arm discontinued due to adverse events. Headache and dizziness caused more dropouts on Tilade than on placebo(7 patients vs 2 for headache, and 6 patients versus 1 for dizziness). No other adverse event showed a clear distinction between the Tilade and placebo in the group that dropped out for adverse events.

Majority of the serious adverse events reported (about 48%) were thought related to asthma exacerbation. These events which included bronchospasm, dyspnea and cough, showed similar frequencies between the active drug and the placebo.

Laboratory assessments did not show any clinically significant changes on Tilade. Also, the post-marketing experience with the Tilade MDI (which was approved in Dec 1992) did not reveal any significant event that would alter the safety pattern seen in current application.

Overall on safety, Tilade Nebulizer Solution at 11 mg three or four times daily and in asthmatics aged 2 and older showed a safety profile consistent with that previously defined by the larger Tilade MDI database. There is a concern that the relatively frequent report of taste perversion might have caused some unblinding of the study, but it is uncertain how the impact of this could be assessed retrospectively.

04 OUTSTANDING ISSUE: LABELING

The draft labeling submitted by the sponsor along with the original NDA was reviewed (see MOR of 8/27/97) and comments were sent to the sponsor asking for a number of changes in the clinical trial sec as well as other sections of the labeling (see telefax of 8/27/97). Subsequently, a telephone confere held to clarify the Division's request on the labeling (see telecon memo of 8/29/97). The spon responded with a new draft labeling incorporating many of the changes requested (submi was reviewed and a new fax was sent to the company requesting some further chan labeling (see telefax of 9/12/97). At this time, the labeling is in the last stages

05 APPROVABILITY

Based on the data submitted by the sponsor and reviewed in this medical officer review, Tilade Nebulizer Solution is approvable for use as a maintenance therapy in mild to moderate asthmatics aged 2 years and older.

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1.0 INTRODUCTION

Tilade inhalation aerosol which contains nedocromil sodium was approved in December 1992 for the preventive management of asthma. The current NDA is for the unit dose of 0.5% nedocromil sodium for nebulization with no excipient. A supplement for the use of the MDI in children (age ≥ 6 years); was recently approved. The current application is for age 2 years and above.

1.1 INDICATION

"Tilade Nebulizer Solution is indicated for maintenance therapy in the management of mild to moderate bronchial asthma in patients aged two and over.

Tilade Nebulizer Solution is NOT indicated for the reversal of acute bronchospasm".

1.2 PROPOSED DOSAGE

"For symptomatic adults and children (aged 2 years and older), the usual starting dosage is the contents of one ampule (11 mg) by nebulization four times a day at regular intervals. In stable asthmatics, it may be possible to reduce Tilade Nebulizer Solution administration to a three times daily regimen for maintenance therapy. For very young children, ages 2 to 5 years with mild asthma and infrequent symptoms, Tilade Nebulizer Solution can be started at a three times daily regimen."

(The recommended dose of Tilade inhaler is 1.75 mg [ex-actuator] QID).

1.3 COMPOSITION

Each 2.2 mL LDPE ampule of Tilade solution contains 0.5% w/v of the drug in water made isotonic with sodium chloride and with pH adjusted to 4.0 - 5.5 using hydrochloric acid. Each ampule contains 11 mg of nedocromil sodium. There are no excipients.

1.4 FOREIGN MARKETING HISTORY

Nedocromil nebulizer solution is approved in Italy (June 1994) and Austria (Feb. 1996).

Tilade MDI is approved and marketed in more than 50 countries including 18 countries where it is also indicated for children. Nedocromil is also available in many countries as Tilade Nasal Spray and Tilade ophthalmic solution.

1.5 CLINICAL DATABASE

The major data supporting the efficacy and safety of Tilade Nebulizer solution are from 16 clinical trials involving the 0.5% nedocromil solution. They include 8 double-blind, randomized, controlled trials carried in the U.S. which the sponsor has designated as pivotal. This Medical officer Review focusses on the 8 U.S pivotal data, in the main. There were 6 other studies which are adequately controlled but non-U.S. Finally, there were two open, long-term safety studies carried out in the U.S. Interestingly, none of the major studies compared Tilade Nebulizer Solution to Tilade MDI. The safety review includes all the 16 studies.

1.6 PIVOTAL STUDIES

The sponsor categorized the pivotal trials into 2 types: "Symptom Reduction Studies" and "Maintenance Studies". The former group of studies enrolled symptomatic patients and assessed the ability of the drug to control their symptoms. The 'Maintenance Studies' included asymptomatic patients who received TID doses of Tilade Nebulizing Solution with the goal of keeping them symptom-free. Tables 1.6A and 1.6B below summarize the major features of the U.S. and non-U.S. clinical trials.

Table 1.6A Eight U.S. controlled studies.

STUDY	DOSING REGIMEN	DURATION	NO. OF PATIENTS	AGE RANGE
SYMPTOM REDUCTION STUDIES				
CR1408	QID	12 Weeks	123	13-70
CR2333	QID	12 Weeks	189	12-81
CR1574	QID	12 Weeks	166	6-12
CR1409	QID	12 Weeks	121	12-70
CR1691	TID	12 Weeks	139	12-67
MAINTENANCE STUDIES				
CR1978	TID	24Weeks	93	6-12
CR2233	TID	12 Weeks	279	2-5
CR3003	TID	12 Weeks	293	5-12

Table 1.6B Six controlled foreign studies.

STUDY	DOSING REGIMEN	DURATION	NO. OF PATIENTS	AGE RANGE
CR1291	QID	12 Weeks	117	26-77
CR1573	QID	8 Weeks	57	2-11
CR2285	TID	12 Weeks	111	2-5
CR2254	TID	12 Weeks	85	2-12
CR1366	BID	12 Weeks	87	16-67
CR1633	QID	Acute	17	19-82

1.7 AUDITING

Limited auditing of the data were carried out by this reviewer and the statistician using the electronic data supplied by the sponsor and the hard copies of the data line listings in the NDA. Given the extensive clinical experience with the Tilade products, a DSI audit was not recommended for this NDA. A number of the investigators who participated in the clinical studies for this application in the U.S. have repeatedly been audited under other NDAs and found acceptable.

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2.0 STUDY CR1408 (vol 1.26, pg 8-16-1 et seq.)

RÉSUMÉ

This was a 12-week randomized, double-blind, placebo-controlled trial in 123 symptomatic adolescent and adult asthmatics aged 12 to 70. The objective was to show that Tilade Nebulizer Solution given at 1 ampule (11 mg) QID could reduce symptoms of asthma. On the primary efficacy variable, the summary symptom score averaged over the last 8 weeks of the trial, Tilade beat placebo with a statistically significant difference. Tilade was also superior to placebo on some secondary endpoints including sleep difficulty and cough severity and nearly so on daytime asthma as well. Although not statistically significant, the objective endpoints of AM PEFR and FEV1, and concomitant medication use all favored Tilade over placebo. On safety, only headache, among the reported adverse events, was more frequently associated with Tilade than placebo. Lab data were within acceptable limits. Overall, this study supports efficacy and safety of Tilade at the dose studied in symptomatic adult asthmatics.

2.1 STUDY DESCRIPTION

DESIGN: Double-blind, randomized, placebo-controlled, 16-week study (12-week treatment period) of 0.5% Nedocromil Sodium (Tilade) Nebulizer Solution (henceforth, Tilade) at doses of 11 mg (1 ampule) QID versus placebo, in asthmatic adult and children (age range 12 to 70 years).
INVESTIGATORS: Five centers: Stanley Gant, Orange, CA; Thomas Hyers, St. Louis, MO; Lawrence Repsher, Wheat Ridge, CO; David Sachs, Palo Alto, CA; Paul Steinberg, Minneapolis, MN.
POPULATION: Patients with chronic airway disease with at least 15% improvement in FEV_1 following a bronchodilator were enrolled. Patients were required to be symptomatic at study entry (but minimal symptom scores were not defined in the protocol).
MATERIALS: Nedocromil (0.5% soln) in 2 mL ampules of 11 mg drug; and matching placebo. The drug or placebo was delivered through a Devilbiss Pulmosonic Nebulizer Device.
OBJECTIVE: To compare Tilade to placebo in patients with reversible obstructive airways disease. The primary efficacy variable was the asthma summary symptom score.
CRITERIA: To be included in the study, patients had to have a diagnosis of chronic, reversible obstructive airways disease defined as paroxysmal attacks of airway obstruction requiring therapy to reverse and be maintained on sustained release theophylline and/or inhaled/oral beta agonist. Pre-bronchodilator FEV_1 should be $>40\%$ predicted. Any abnormal lab value disqualified patients from the study. Also excluded were patients who had received oral or parenteral steroids for >10 days within 3 months of the study; patients who had required both oral steroids within 4 weeks and inhaled steroids within 2 weeks of the study; or cromolyn within 1 month of the study.
CONCOMITANT MEDs: Inhaled beta agonist (Ventolin MDI) as needed for bronchospasm, immediate-release theophylline(max:q6h), mucolytics and expectorants, topical nasal steroids, decongestants, Nasalcrom and Opticrom; and antibiotics. Oral steroids were disallowed.
CONDUCT: There was a 2-week run-in period followed by a 2-week baseline period after which patients were randomized into the study to receive either Tilade or placebo four times per day for a 12-week period. Clinic visits occurred at study entry, 2 weeks after entry, at the start of the double-blind period and every 2 weeks during the treatment period. Patients used daily diary records to record AM and PM PEFR, daytime and cough symptom scores(both scored daily), nighttime asthma severity scores and use of study drug and concomitant medications. At the screening visit (visit 1, week 0), patients had hx, physical exam, PFTs and labs (blood and urine, preg test etc.), and evidence of 15% reversibility in FEV_1 with those with normal results proceeding to the run-in phase. During this phase, patients were screened for symptoms, and supplied with a diary card and a peak flow meter to record their symptoms and PEFR. Visit 2 started

the 2-week baseline period during which patients continued to record their symptoms, monitor drug use and record any adverse events. Visit 3 was the start of the double-blind period. To be eligible for randomization, a patient must have had a sum total of ≥3 on daytime asthma and sleep difficulty scores for at least 7 days out of the 14 baseline days. The symptoms rated by the patient included daytime asthma severity, sleep difficulty due to asthma and cough. Daytime asthma and cough were scored on a scale of 0 to 4 for none, mild, moderate, severe and very severe. Sleep difficulty due to asthma was scored on a 3-point scale: 0=slept well, no asthma; 1=woke once because of asthma; 2=woke more than once because of asthma. The scores were recorded in the daily diary throughout the 12-week treatment period. In addition, patients also recorded daily their use of treatment drugs and concomitant medications, and AM and PM PEFR. Other assessments during the study included PFTs, investigator rating of patient's severity of asthma on 0 to 4 scale, both at each 2-weekly visit. Also, at the final visit (week 12), the investigator rated the overall effectiveness of the treatment as 1=very effective, 2=moderately effective, 3=slightly effective, 4=no effect, or 5=made condition worse. Adverse events were elicited by questioning during each of the clinic visits and recorded by the investigator in the CRF.

DATA ANALYSIS The protocol-defined primary efficacy variable was the summary symptom score derived by adding the scores on daytime asthma severity, and on sleep difficulty due to asthma. The protocol-defined period for analysis was the last 8 weeks of the trial: weeks 5 to 12. The primary analysis was a non-parametric analysis whereby the scores were converted to ranks separately for each of the two symptoms and then averaged and analyzed. Additionally, a parametric analysis was carried out at the request of the Division. Efficacy analyses were also carried out on the PFT variables (FEV_1, PEFR, FVC and $FEF_{25-75\%}$); and the investigator rating of the severity of patient's asthma. Safety variables included adverse event recordings, and also blood and urine lab measurements at baseline and at week 12.

2.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total screened			156
Total Randomized	60	63	123
Completed	56	56	112
Total dropouts	4	7	11
Dropout due to adverse event	2	3	
Dropout due to treatment failure	0	0	
Dropout due to non-compliance	1	0	
Dropout due to loss to follow-up	1	4	
Dropout due to intercurrent illness	0	0	
Dropout due to intolerance of study drug	0	0	
Efficacy Analysis population	58	60	118
Safety Analysis population (Intent-to-Treat)	60	63	123

Patient Characteristics

A total of 123 patients were randomized to treatment out of 156 patients screened. Data from 5 patients (2 Tilade and 3 placebo) were completely excluded from the efficacy analysis, leaving 118 patients in that subset: 58 on Tilade, 60 on placebo. Of the 5 (exclusions for whom no data were available), all 3 placebo cases were due to loss to follow-up while 1 Tilade patient was unco-operative and another withdrew after 3 days. In addition to these complete exclusions, 5 other patients had partial data exclusion due to incomplete participation in the study.

Of the 118 patients, 77 were male and 41 were female. There was a disparity in the male:female ratio between the Tilade and the placebo groups: 57%:43% on Tilade versus 73%:27% on placebo. Age range for the efficacy population (n=118) was 13-70 years, mean was 35 years for Tilade and 36.8 years for the placebo.

2.3 EFFICACY RESULTS

The primary efficacy variable is the summary symptom score which combines the scores for the daytime asthma severity and sleep difficulty into one composite score. Daytime asthma severity was scored on a scale of 0 to 4 for none, mild, moderate, severe and very severe while sleep difficulty was scored on 0 to 2 for no awakening, one awakening, and >1 awakening due to asthma. The summary symptom therefore had a possible maximum score of six points.

Table 2.3.1A below shows the mean baseline summary symptom score and the mean scores over the 1-12 week study period, as well as 5-12 week period (Intent to treat with LOCF). The latter interval is the protocol-defined primary endpoint.

Table 2.3.1A. Adjusted mean values (adjusted for baseline, center and treatment) for Summary Symptom Score, and change from baseline. Parametric analysis.

	TILADE (n=57)	PLACEBO (n=60)	*p*-value
Baseline	3.55	3.44	0.397
Week 1-12	2.32	2.82	0.021
Week 5-12*	2.33	2.73	0.034
Change from baseline (over week 5-12)**	-1.23	-0.78	0.034

* data from table on page 8-16-8 vol 1.26 based on protocol-defined WOCF analysis

** these values are least square means adjusted for center and baseline (and differ slightly from the sponsor's unadjusted values contained on page 8-16-15, vol 1.26)

Table 2.3.1B below contains figures based on the protocol-defined analysis which assigned the worst observation to dropouts (WOCF) rather than the post-hoc LOCF-based analysis requested by the Division and used to calculate the main efficacy variables.

Table 2.3.1B. Two-weekly means of summary symptom scores, compared using ANOVA. Intent-to-treat analysis with protocol-defined WOCF. Parametric analysis.

	TILADE (n=58)	PLACEBO (n=60)	*p value*
Baseline	3.58	3.44	0.397
Week 1-2	2.72	3.07	0.045
Week 3-4	2.45	2.89	0.036
Week 5-6	2.36	2.88	0.011
Week 7-8	2.20	2.77	0.018
Week 9-10	2.33	2.65	0.160
Week 11-12	2.62	2.27	0.136
Week 5-12	2.28	2.73	0.034

Based on the results in tables 2.3.1A and B above, Tilade showed a statistically significant improvement over placebo. The size of the difference is modest: approximately 0.4 on a 6-point scale if one considers the mean values averaged over weeks 5 to 12, or about 0.45 based on the change from baseline.

Table 2.3.1B also shows that the response to therapy on Tilade was not consistent throughout the study period. While Tilade was superior to placebo in the first 8 weeks of treatment, there was no significant difference between the two in the last 4 weeks. This is largely due to the daytime asthma scores failing to achieve significance after week 7, while the nighttime scores continued to favor the active drug. Since the dropout number was small (only 4 on Tilade), this may not be just due to sample size. Based on this primary efficacy analysis therefore, Tilade showed efficacy in the first week but this lasted only 8 weeks into the study.

Table 2.3.1C below shows a categorical analysis of the response of the patients (based on the summary symptom score) over the week 5-12 period. The analysis was carried out (using the SAS data set provided by the sponsor) by this reviewer and the statistician (Dr. Bono). The "standardized score" was derived by dividing the mean change from baseline in summary symptom scores by the albuterol use score. The albuterol use score was defined in the protocol as one point for each dose (=2 puffs) of rescue Ventolin MDI used by the patient during the treatment period under consideration (weeks 5-12). The standardized scores were grouped into 3 categories: <0; 0 to 0.75 and >0.75 in order to have a sufficient number of patients in each category for statistical comparison. This *post-hoc* categorical analysis shows that when albuterol use was factored in, patients on Tilade had higher mean change in summary symptom scores (that is they sustained greater improvement) compared to placebo patients. Tilade had three times more patients who improved by >0.75 standardized symptom score compared to placebo. The overall response favored Tilade statistically, $p<0.02$.

Table 2.3.1C. Standardized Symptom Scores*.

Standardized Symptom Scores ⇨	<0	0-0.75	>0.75
Tilade (n=57)	11	28	18
Placebo (n=57)	13	38	6

*a post-hoc variable computed by dividing the mean change from baseline in summary symptom score over weeks 5 to 12 by the rescue Ventolin-use score. Only patients with baseline and complete diary symptom records are included in this analysis (i.e. study completers).

2.3.2 SECONDARY EFFICACY VARIABLES

2.3.2.1 PATIENT-RATED SYMPTOMS

As shown in table 2.3.2.1 below, Tilade showed statistically significant superiority over placebo on sleep difficulty and cough severity. On daytime asthma, the difference numerically favor Tilade but was short of statistical signficance.

Table 2.3.2.1 Baseline and On-study averages of patient-rated symptoms

	TILADE (n=58)	PLACEBO (n=60)	*p* value
SLEEP DIFFICULTY			
Baseline	1.20	1.10	
Week 5-12 average	0.70	0.92	0.019
DAYTIME ASTHMA			
Baseline	2.38	2.35	
Week 5-12 average	1.58	1.81	0.095
COUGH SEVERITY			
Baseline	1.58	1.52	
Week 5-12 average	0.88	1.32	0.005

2.3.2.2 ADDITIONAL SECONDARY VARIABLES: Pulmonary Function & Concomitant Meds

Patients were required to measure and record their PEFR twice daily. Pulmonary Function Tests were measured at each visit. As shown in table 2.3.2.2 below, Tilade was marginally superior to placebo on AM PEFR with the difference approaching statistical significance, but there was no statistically significant difference between the two study arms on FEV_1.

A scoring system was used for assigning a score to the concomitant medications. Each of the following was assigned one point:

- patient's individualized starting dose of theophylline (e.g. 250 mg);
- one tablet of an oral bronchodilator;
- 2 puff dose of a bronchodilator;
- a unit dose of prednisone (e.g. 5 mg)

The patients recorded their use of these concomitant medications and in their diary and the number of points were added for the last 8 weeks of the treatment period.

TABLE 2.3.2.2 PFTs and Concomitant Medication

	TILADE (n=58)	PLACEBO (n=60)	*p value*
AM PEFR			
Baseline	348.9	369.2	
Week 5-12 average	382.4	362.3	0.055
FEV_1			
Baseline	2.40	2.59	
Week 5-12 average	2.50	2.65	0.122
CONCOMITANT MEDS			
Baseline	5.13	4.79	
Week 5-12 average	4.17	4.66	0.061

CONCLUSIONS ON EFFICACY

In this study, Tilade demonstrated a small but statistically significant superiority over placebo on the primary efficacy variable (summary symptom score over weeks 5 to 12). Analysis of the two-weekly averages of the summary symptom score showed that Tilade established superiority over placebo within the first 2 weeks, but this superiority disappeared after week 8 as the placebo symptom scores improved while Tilade scores worsened. The reason for this anomaly is unclear. A *post-hoc* categorical analysis showed that with the use of rescue Ventolin factored into the response, significantly more patients on Tilade than on placebo had substantial improvement in their summary symptoms over the week 5-12

period. On the secondary variables, Tilade beat placebo on nighttime asthma, cough severity and AM PEFR but not on FEV_1, daytime asthma or concomitant medication use, although the latter approached statistical significance. Overall, this study provides reasonable evidence of efficacy for Tilade in the population studied.

2.4 SAFETY RESULTS

2.4.1 ADVERSE EVENTS (AE's)

Adverse event information were collected by questioning the patients at clinic visits. Table 2.4.1 below shows the major AE's recorded during the study. AE's were selected for inclusion (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on placebo or only occurred in one patient were excluded from this list. Based on this table, only headache stands out as an AE that occurred more frequently on drug than on placebo. Others such as hypesthesia, diarrhea, pain and eye itching occurred only on Tilade but in only two patients each, making conclusion on causality or possibly drug-relatedness difficult.

Table 2.4.1 Occurrence of AE's

ADVERSE EVENT	TILADE (n=60)	PLACEBO (n=63)
Headache	18%	11%
Chest pain	10	19
Coughing	8	13
Rhinitis	7	11
Bronchospasm	7	8
Dyspnea	3	10
URI	5	8
Sinusitis	7	5
Dyspepsia	6	6
Nausea	3	6
Mouth dryness	5	3
Taste perversion	3	2
Hypesthesia	3	0
Diarrhea	3	0
Pain	3	0
Eye itching	3	0

2.4.2 Discontinuations due to Adverse Events

Five patients dropped out of the study due to adverse events; two were on Tilade and three on placebo. One patient on Tilade had worsening asthma on day 13, while the other had severe headache on day 4. The placebo patients dropped out due to chest congestion, worsening asthma and nasal congestion/chest tightness respectively. No deaths were reported during the study.

2.4.3 Laboratory Data

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and at the last study visit. Tests done included hematology and chemistry. The only measurement that changed from baseline to end of the study with a statistically significant difference between Tilade and placebo was the platelet count. Placebo mean counts rose from 251,000/mm^3 to 270,000 while Tilade mean counts fell from 267,000 to 256,000. Although the *p value* comparing the two arms was 0.02, this difference and the slight fall in platelet count seen on Tilade are unlikely to be of clinical significance.

CONCLUSIONS ON SAFETY

The safety picture for Tilade seen in study 1408 is compatible with the profile that has been demonstrated for the drug with the MDI. Adverse events were minimal, and only headache appears to stand out. None of the other complaints could be causally attributed to the drug. The lab data showed no clinically significant abnormality. Overall, the safety of Tilade, based on the data in this study, is within acceptable limits.

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3.0 STUDY CR 2333 (vol 1.32, pg 8-22-15 et seq., data tables in vol 1.38)

RÉSUMÉ

This 'symptom reduction' 12-week trial was carried out in 189 in symptomatic adolescent and adult asthmatics comparing Tilade given at 1 ampule (11 mg) QID with placebo. On the primary efficacy endpoint, the combination of summary symptom score and concomitant medication averaged over weeks 3-12, Tilade beat placebo but did not make the statistically significant level (p=0.06). When the variables were averaged over the 12 week duration of the study however, Tilade was significantly superior to placebo on the combined endpoint as well as on summary symptom score. Small and borderline results were also seen on the secondary endpoints including sleep difficulty and daytime cough. Safety assessments were within acceptable limits. Based on a strict application of the protocol-defined endpoint, this study failed to support the efficacy of Tilade over placebo. A marginal success was however discernable based on the numerical trend in the data.

3.1 STUDY DESCRIPTION

This study had the same protocol as study CR 1408, except for some variations noted below. It was a double-blind, randomized, placebo-controlled, 16-week study (12-week treatment period) of 0.5% Nedocromil Sodium (Tilade) Nebulizer Solution at a dose of 11 mg (1 ampule) QID versus placebo, in asthmatic adult and adolescents (age range 12 to 70 years). There were 8 study centers: Stanley Gant, Orange, CA; Jyothi Gadde, Greenbelt, MD; Michael Kraemer, Spokane, WA; Michael Noonan, Portland, OR; Loren Southern, Princeton, NJ; James Taylor, Tacoma, WA; Robert Webb, Kirkland, WA; Steven Weinstein, Hunting Beach, CA. The study was conducted from July 1992 to May 1993. In addition to the other entry conditions described in CR1408, patients were required to have FEV_1 between 50-80% predicted, a minimum score of 3 for daytime plus sleep difficulty scores (a 0 to 6 scale) for at least 7 of the 14 baseline days.

There was a 2-week baseline period, after which patients were randomized to receive either Tilade or placebo four times per day for a 12-week period. Clinic visits occurred at study entry, and after 2,4,6,8 10 and 12 weeks of treatment. Patients used daily diary records to record AM and PM PEFR, daytime asthma severity, sleep difficulty due to asthma, daytime cough, and the use of study drug and concomitant medications. Daytime asthma and cough were both scored on a scale of 0 to 4 for none, symptoms (or cough) barely noticeable, symptoms noticeable but not bad enough to interfere with daily routine, symptoms noticeable enough to interfere with daily routine, symptoms present most of the day and radically changed daily routine. Sleep difficulty due to asthma was scored on a 3-point scale: 0=slept well, no asthma; 1=woke once because of asthma; 2=woke more than once because of asthma. Other assessments during the study include PFTs, investigator rating of patient's severity of asthma on 0 to 4 scale (same scale as used by the patient for daytime symptom score), both at each 2-weekly visit. At the final visit (week 12), the patient and investigator rated the overall effectiveness of the treatment as 1=very effective, 2=moderately effective, 3=slightly effective, 4=no effect, or 5=made condition worse. Adverse event were elicited by questioning during each of the clinic visits and recorded by the investigator in the CRF.

The protocol-defined primary efficacy variable was the combination of 1) summary symptom score (sum of daytime asthma severity, and sleep difficulty due to asthma); and 2) concomitant medication use. The protocol-defined period for analysis was the last 10 weeks of the trial: weeks 3 to 12. The primary analysis

was a rank-transformed analysis of covariance (ANCOVA). Additionally, a parametric analysis of covariance was carried out on the primary variables. Efficacy analyses were also carried out on the PFT variables (FEV_1, PEFR, FVC and $FEF_{25-75\%}$); investigator rating of the severity of patient's asthma. Safety variables included adverse event recordings, blood and urine labs at baseline and at week 12.

3.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total screened			264
Total Randomized	94	95	189
Completed	86	82	168
Total dropouts	8	13	21
Dropout due to adverse event	3	4	
Dropout due to treatment failure	1	2	
Dropout by patient request	1	2	
Dropout due to loss to follow-up	1	3	
Dropout by patient request + AE	1	0	
Dropout by patient request + treatment failure	1	0	
Dropout due to treatment failure + AE	0	1	
Dropout by patient request + loss to follow-up		1	
Efficacy Analysis population	94	92	186
Safety Analysis population (Intent-to-Treat)	94	94	188

Patient Characteristics

A total of 189 patients were randomized to treatment out of 264 patients screened. One patient was lost to follow-up immediately after randomization; 188 patients constituted the study population. Of these 188 patients, 103 were male and 85 were female. Data from 3 patients (all on placebo) were completely excluded from the efficacy analysis, leaving 186 patients of the randomized 189 patients in the efficacy subset: 94 on Tilade, 92 on placebo. One of the 3 patients had data only up to visit 2; one had only one day of double-blind treatment and the third did not return for follow up after randomization. Age range for the efficacy population was 12-81 years, mean was 31.5 years for Tilade and 34.6 years for the placebo group. Mean baseline symptom scores were 3.41 for Tilade and 3.33 for placebo, and baseline FEV_1 was 2.45 and 2.39 L, respectively.

A total of 31 patients were regarded as 'treatment failures', including the 3 who actually dropped out of the study, and those who took disallowed medications. There were 12 on Tilade and 19 on placebo.

3.3 EFFICACY RESULTS

The primary efficacy variable is the combination of the summary symptom score (the sum of the scores for the daytime asthma severity and sleep difficulty) and the concomitant medication use score. The primary time period for efficacy analysis was weeks 3 to 12.

Table 3.3.1A shows the mean data for the summary symptom score, the concomitant medication scores and the average of the two. For each variable the mean is shown at baseline, averaged over the primary efficacy period (weeks 3 to 12) and over the entire study period. The placebo patients used more concomitant medications at baseline, the difference approaching statistical significance (p=0.06). Over the treatment period, Tilade was significantly superior to placebo on symptom scores but not on concomitant medical scores. On the combined score over weeks 3-12, which is the primary endpoint, Tilade was numerically better than placebo, but the difference merely approached statistical significance (p=0.06). The data shown in table 3.3.1A employed a worst-observation-carried-forward (WOCF) analysis. A similar ANOVA analysis using LOCF (as contained in the statistician's review) showed a significant difference favoring Tilade over placebo on the primary endpoint.

Table 3.3.1A Mean baseline and on-study data for the primary efficacy variables, WOCF, ANOVA analysis. (On-study means are adjusted for baseline and center).

		TILADE		PLACEBO		*p value*
		n	MEAN	n	MEAN	
Summary symptom score	Baseline	94	3.41	94	3.33	0.51
	Weeks 3-12	89	2.49	86	2.95	0.03
	Weeks 1-12	89	2.50	86	2.97	0.018
Concomitant medication score	Baseline	94	2.66	94	3.15	0.06
	Weeks 3-12	87	2.46	83	2.61	0.31
	Weeks 1-12	89	2.43	86	2.69	0.19
Combined endpoint* score	Baseline	94	4.79	94	4.70	0.66
	Weeks 3-12	89	2.50	86	2.83	0.06
	Weeks 1-12	90	2.46	88	2.87	0.03

* mean of symptom scores and concomitant medical scores.

Table 3.3.1B below (extracted from vol. 1.38 pages 8-28-410 et seq.) shows the mean scores for the combined (averaged) summary symptom score plus concomitant medication use over each 2-week period of the study. The response to therapy on Tilade was not consistent throughout the study period. While Tilade was superior to placebo in the first 6 weeks of treatment, there was no significant difference between the two in the last 6 weeks. This may account for the inability of Tilade to beat placebo when the data was averaged over weeks 3 to 12 as seen in table 3A above.

Table 3.3.1B Two-weekly means of combined summary symptom scores and concomitant medication use (ANOVA. WOCF. Parametric analysis).

	TILADE		PLACEBO		*p value*
	n	MEAN	n	MEAN	
Baseline	94	4.79	94	4.70	0.66
Week 1-2	94	2.52	91	2.96	0.005
Week 3-4	92	2.29	88	2.89	0.002
Week 5-6	91	2.43	88	2.85	0.02
Week 7-8	89	2.61	86	2.85	0.28
Week 9-10	88	2.58	84	2.85	0.08
Week 11-12	87	2.55	83	2.79	0.30

3.3.2 SECONDARY EFFICACY VARIABLES

3.3.2.1 PATIENT-RATED SYMPTOMS

Patients recorded their level of asthma-related symptoms in their diaries on scales described in the study design section above. Table 3.3.2.1 below shows the mean baseline symptom scores and on-study mean averaged over the primary efficacy period, weeks 3-12. On these individual symptoms, Tilade beat placebo at a statistically significant level only on sleep difficulty, although the trend favored Tilade on both daytime asthma and daytime cough as well.

TABLE 3.3.2.1. Mean values of patient-rated symptoms.

	TILADE		PLACEBO		*p value*
	n	MEAN	n	MEAN	
SLEEP DIFFICULTY					
Baseline	89	0.97	86	0.97	
Week 3-12 average	89	0.70	86	0.89	0.03
DAYTIME ASTHMA					
Baseline	89	2.41	86	2.34	
Week 3-12 average	89	1.79	86	2.04	0.11
DAYTIME COUGH					
Baseline	89	1.39	86	1.35	
Week 3-12 average	89	1.04	86	1.32	0.08

3.3.2.2 ADDITIONAL SECONDARY VARIABLES: Pulmonary Function

Patients measured and recorded their PEFR twice daily. Pulmonary Function Tests were recorded at each visit. As shown in table 3.3.2.2 below, Tilade was superior to placebo on AM PEFR and on FEV_1, although the differences are really small.

TABLE 3.3.2.2 PFTs and Concomitant Medication

	Tilade	Placebo	P value
AM PEFR	(n=80)	(n=74)	
Baseline	391.5	378.1	
Week 3-12 average	411.0	390.1	0.05
Week 1-12 average	409.9	390.3	0.04
FEV_1	(n=89)	(n=85)	
Baseline	2.49	2.42	
Week 3-12 average	2.62	2.54	0.05

('n' values as stated in the table are those at baseline).

CONCLUSIONS ON EFFICACY

In this study, Tilade demonstrated a small superiority over placebo. Over the primary analysis time-period (weeks 3 to 12), this difference approached statistical significance on the primary endpoint - combined summary symptom score and concomitant medication use - ($p=0.06$), and actually achieved statistical significance on the symptom scores ($p=0.03$), but not on concomitant medication. The placebo patients were on slightly higher amount of concomitant medication at baseline, and were able to reduce the use of concomitant therapy more than the Tilade group was able to. This blunted the superiority of Tilade over placebo on the primary efficacy variable which combined the summary symptom score with concomitant medication use. Among the secondary efficacy variables, sleep difficulty, AM PEFR and FEV_1 favored Tilade. Overall, this study supports the efficacy of Tilade, although the margin was narrow on many of the endpoints.

3.4 SAFETY RESULTS

3.4.1 Adverse Events (AE's)

Adverse event information were collected by questioning the patients at clinic visits. A total of 188 patients (94 per arm) were included in the safety analysis; only one patient (out of the 189 randomized) who was lost to follow-up after randomization, was excluded. One hundred and sixty-nine (169) patients reported at least one AE; 85 in the Tilade group and 84 on placebo. Table 3.4.1 below shows the major AE's recorded during the study. AE's were selected for inclusion in this table (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on placebo or only occurred in one patient were excluded from this list. Although URI was the most commonly reported AE, its occurrence was almost equal between Tilade and placebo. Bronchitis and unpleasant taste stand out as two notable AE's that occurred more frequently on active drug than on placebo.

Table 3.4.1 Occurrence of the AE's

ADVERSE EVENT	TILADE (n=94)	PLACEBO (n=94)
URI	39%	37%
Bronchospasm	14	26%
Pharyngitis	19	14
Sinusitis	17	13
Bronchitis	12	6
Unpleasant taste	6	2
Gastroenteritis	4	3

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Table 3.4.1 Occurrence of the AE's cont'd

ADVERSE EVENT	TILADE (n=94)	PLACEBO (n=94)
Dizziness	3	3
Arthralgia	2	2
Hypertonia	2	0
Rash	1	1
Tremor	1	0
Dry mouth	1	0

3.4.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

Twelve patients dropped out of the study due to adverse events; five on Tilade and seven on placebo. Table 3.4.2 below shows the AE's leading to withdrawal from the study for the 12 patients. None of the causes of withdrawal on Tilade appeared particularly unusual. No deaths were reported during the study.

Table 3.4.2 Dropouts due to Adverse Events

	DURATION	SEVERITY	DAYS ON STUDY
TILADE			
Headache	not stated	moderate	10
Headache / Dizziness	72 hours / 6 weeks	severe / mild	41
Sinusitis	12 days	moderate	26
Asthma exacerbation	12 days	severe	25
Dizziness/Headache	7 days	severe	7
PLACEBO			
Uterine fibroid	2 months	mild	1
Asthma exacerbation	4 months	severe	43
Pneumonia	9 days	severe	42
Acute asthma	2 hours	very severe	1
UBI / Asthma exacerbation	9 days / 16 days	severe	2
Asthma exacerbation	14 days	severe	31
Asthma exacerbation	4 days	very severe	17

3.4.3 LABORATORY DATA

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and at the last study visit. Tests done included blood biochemistry, hematology and urinalysis. In the Tilade arm, a few measurements (i.e. MCH, MCHC, uric acid, and urine specific gravity) were significantly changed from baseline. However, only the change in MCH was statistically different ($p=0.05$) when compared to the change on placebo. This difference and the slight fall in MCH seen on Tilade (from 30.1 at baseline to 29.7 pg at study-end) are unlikely to be of clinical significance.

CONCLUSIONS ON SAFETY

The safety profile for Tilade Nebulizer Solution seen in study 2333 is comparable to that demonstrated for MDI formulation of the drug. Adverse events were strikingly minimal in this study and none of those reported appeared unusual for this drug. The lab data showed no clinically significant abnormality. Overall, the safety of Tilade, based on the data in this study, is within acceptable limits.

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4.0 STUDY CR 1574 (vol 1.42, pg 8-32-36 et seq)

RÉSUMÉ

This 12-week 'symptom reduction' study in 166 asthmatic children aged 6 to 12 years employed a pre-specified but 'unusual' endpoint: the Worst Symptom score. On this variable, defined as the score on the most troublesome symptom during the baseline period, Tilade given at 1 ampule (11 mg) QID over 12 weeks showed a statistically significant efficacy over placebo. Tilade also beat placebo on the other symptoms such as daytime asthma, cough as well as on AM PEFR. Safety profile in this young population was similar to that seen in the other pediatric and in the adult trials. Overall, a positive study.

4.1 STUDY DESCRIPTION

This study in pediatric patients had the same protocol as study CR 2333, except for some variations noted below. It was a double-blind, randomized, placebo-controlled, 14-week study (12-week treatment period) of 0.5% Nedocromil Sodium (Tilade) Nebulizer Solution at doses of 11 mg (1 ampule) QID versus placebo, in asthmatic children (age range 6-12 years). There were 7 study centers: Edwin Bronsky, Salt Lake City, UT; Robert Dockhorn, Prairie, KS; Elliot Ginchansky, Dallas, TX; Michael Kraemer, Spokane, WA; David Pearlman, Denver, CO; Paul Ratner, San Antonio, TX; William Storms, Colorado Springs, CO. The study was conducted from March 1990 to February 1991.

The most significant difference in the design of this study compared to the other studies of 'symptomatic' patients (CR 1408, CR 2333, etc.), is in the primary efficacy variable. The primary variable was based on the diary scores of the symptom which was most troublesome to the patient during the baseline period (i.e. the worst symptom). A statistically significant improvement in the worst symptom on Tilade compared to placebo was to be regarded as a positive outcome. Patients were required to have a (15%) reversibility in FEV_1, greater than 40% predicted FEV_1 at enrolment and a symptom score of 2 or more on an individual symptom on a 4-point scale as described below.

There was a 2-week baseline period, after which patients were randomized to receive either Tilade or placebo four times per day for a 12-week period. Clinic visits occurred at study entry, and after 2,4,8 and 12 weeks of treatment. Patients used daily diaries to record AM and PM PEFR, daytime and cough symptom scores(both scored daily), and nighttime asthma severity scores. Daytime asthma and cough were both scored on a scale of 0 to 4 for 0=none, 1=symptoms (or cough) barely noticeable, 2=symptoms noticeable but not bad enough to interfere with daily routine, 3=symptoms noticeable enough to interfere with daily routine, and 4=symptoms present most of the day and radically changed daily routine. Nighttime asthma was scored on a 4-point scale: 0=no symptoms; 1=woke once because of asthma and returned to sleep in <1 hour; 2=woke once, used escape medication and returned to sleep in less than one hour; 3=awoke once but remained awake >1 hour because of continuing symptoms; 4=awake most of the night because of asthma. Other assessments during the study included PFT at each visit, and investigator rating of patient's severity of asthma on 0 to 4 scale (none, mild, moderate, severe and very severe). At the final visit (week 12), the patient, parent and investigator rated the overall effectiveness of the treatment as 1=very effective, 2=moderately effective, 3=slightly effective, 4=no effect, or 5=made condition worse. Adverse event were elicited by questioning during each of the clinic visits and recorded by the investigator in the CRF.

The protocol-defined primary efficacy variable was the worst symptom, defined as the symptom which scores 2 or higher for the greatest number of days during the 2 week baseline period. If 2 or more symptoms tied, the symptom with the highest average score during the baseline period was selected, or if the tie persisted, the following ordering was used: daytime asthma, nighttime asthma and cough. Secondary efficacy endpoints included individual diary scores for daytime asthma, nighttime asthma, cough, use of bronchodilators, AM and PM PEFR. Efficacy analyses were also carried out on the PFT variables (FEV_1, PEFR, FVC and $FEF_{25-75\%}$).

The protocol-defined period for analysis was the last 10 weeks of the trial: weeks 3 to 12. The primary analysis was a rank-transformed non-parametric analysis of covariance (ANCOVA) of the change from baseline on the efficacy variables. Parametric analyses of covariance of the original data were also carried out. Safety variables included adverse event recordings, blood and urine labs at baseline and at week 12.

4.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total screened			197
Total Randomized	81	85	166
Completed	68	77	145
Total dropouts	13	8	21
Dropout due to non-compliance	4	1	
Dropout due to treatment failure	4	1	
Dropout for personal reasons	1	2	
Dropout due to adverse events	1	1	
Dropout due to intercurrent illness	1	1	
Dropout due to protocol violation	0	1	
Dropout due to loss to follow-up	0	1	
Dropout due to move outside trial area	1	0	
Dropout due to other reasons	1	0	
Efficacy Analysis population	79	83	162
Safety Analysis population (Intent-to-Treat)	80	83	163

Patient Characteristics

A total of 166 patients were randomized to treatment out of 197 patients screened. Data from 3 patients (one on Tilade, 2 on placebo) were completely excluded from the efficacy analysis because the patients did not receive study treatment. One additional patient who received treatment only for 4 days was excluded. These exclusions left 162 of the randomized 166 patients in the efficacy subset: 79 on Tilade, 83 on placebo. Of the 162 patients who constituted the efficacy population, 121 were male and 41 were female. Age range for this efficacy population was 6-12 years, mean was 9.5 years for Tilade and 9.1 years for the placebo group. Mean baseline daytime symptom score was 1.94 for both Tilade and placebo, and baseline FEV_1 was 1.67 and 1.60 liters, respectively.

A total of 31 patients were regarded as 'treatment failures', including the 3 who actually dropped out of the study, and those who took disallowed medications. There were 12 on Tilade and 19 on placebo.

4.3 EFFICACY RESULTS

The primary efficacy variable was the diary scores of the worst symptom, i.e. the most troublesome score during the baseline period. The primary time period for efficacy analysis was weeks 3 to 12.
For the majority of the patients, the daytime asthma symptom was the most troublesome. Indeed, 71% of the Tilade patients and 70% of the placebo patients had daytime asthma as the worst symptom. About 24% of patients on each arm rated cough as the most troublesome symptom, while only 5% and 6% respectively chose nighttime symptom as the most troublesome.

Table 4.3.1A (from vol 1.42 pg 8-32-77) shows the mean data for the worst symptom: at baseline, over the main efficacy period (weeks 3 - 12) and the size of the change from baseline. From baselines that were comparable, Tilade had greater improvement in the worst symptom over the primary efficacy period compared to placebo. This difference is statistically significant, thus supporting the efficacy of Tilade on this variable.

Table 4.3.1A Mean baseline and on-study data for the primary efficacy variable- the Worst Symptom. LOCF, ANCOVA, Parametric analysis. Means are unadjusted.

WORST SYMPTOM	TILADE (n=79)	PLACEBO (n=83)	*p value*
Baseline	2.06	2.02	
Mean weeks 3-12	1.20	1.51	
Change from baseline	-0.84	-0.52	0.025

Table 4.3.1B below (extracted from vol. 1.42 pages 8-32-77.) shows the mean scores for the worst symptom over each 2-week period of the study. Unlike the pattern in adult studies CR 1408 and CR 2333, Tilade became superior to placebo early in the study (week 1-2) and maintained this superiority throughout the study period (except at week 11-12 interval, when the difference was short of statistical significance). A trend towards improvement was also visible in the placebo group, with the worst symptom progressively improving during the course of the study. This suggests that part of the response seen on Tilade was likely due to a placebo response. Nonetheless, this analysis supports the efficacy of Tilade over placebo.

Table 4.3.1B Two-weekly means of the scores on the Worst Symptom

	TILADE (n=79)	PLACEBO (n=83)	*p value*
Baseline	2.06	2.02	
Week 1-2	1.57	1.75	0.053
Week 3-4	1.33	1.60	0.021
Week 5-6	1.16	1.52	0.005
Week 7-8	1.16	1.54	0.008
Week 9-10	1.18	1.47	0.035
Week 11-12	1.19	1.39	0.094

4.3.2 SECONDARY EFFICACY VARIABLES

4.3.2.1 PATIENT-RATED SYMPTOMS

In addition to the Worst Symptom discussed above, analysis of the individual symptoms was also carried out. As shown in table 4.3.2.1 below, Tilade was more efficacious than placebo in improving daytime symptoms and cough. There was however no significant difference between the two arms on nighttime asthma symptom, although the numerical trend favored Tilade. These findings support the efficacy of Tilade in the two symptoms (daytime asthma, and cough) that patients found most troublesome during the baseline period.

TABLE 4.3.2.1 Mean values of patient-rated symptoms.

	TILADE		PLACEBO		*p value*
	n	Mean	n	Mean	
DAYTIME ASTHMA					
Baseline	79	1.94	83	1.94	
Week 3-12 average	76	1.18	80	1.46	0.043
NIGHTTIME ASTHMA					
Baseline	79	1.04	83	1.09	
Week 3-12 average	75	0.63	80	0.90	0.147
COUGH					
Baseline	79	1.48	83	1.61	
Week 3-12 average	76	0.82	80	1.25	0.006

4.3.2.2 ADDITIONAL SECONDARY VARIABLES: Pulmonary Function & Bronchodilator Use.

Patients measured and recorded their PEFR twice daily. Pulmonary Function Tests were recorded at each visit. As shown in table 4.3.2.2 below, Tilade only beat the placebo on AM PEFR. And although the trend was in favor of Tilade on FEV_1, there was no statistically significant difference between the two arms of the study on this variable and on bronchodilator use.

TABLE 4.3.2.2 PFTs and Concomitant Medication

	TILADE	PLACEBO	*p value*
AM PEFR *(L/min)*	(n=78)	(n=83)	
Baseline	250.5	244.0	
Week 3-12 average	264.6	243.2	
Change from baseline	13.6	-0.2	0.019
FEV_1 *(L)*	(n=78)	(n=81)	
Baseline	1.67	1.60	
Week 3-12 average	1.70	1.58	
Change from baseline	0.03	-0.02	0.102
BRONCHODILATOR USE *(times/day)*	(n=79)	(n=83)	
Baseline	4.0	3.8	
Week 3-12 average	3.3	2.9	
Change from baseline	-0.6	-0.8	0.218

('n' values as stated in the table are those at baseline).

4.3.3.3 ADDITIONAL SECONDARY VARIABLES: Clinical Assessments by the Investigator, and by clinician, patient and parent

The investigator assessed the asthma severity at each clinic visit on a scale of 0 to 4, for none to very severe. As shown in table 4.3.3.3 below, Tilade beat the placebo consistently at each visit except at week 12. Tilade was also superior when these scores were averaged over weeks 4 to 12.

TABLE 4.3.3.3 INVESTIGATOR ASSESSMENT OF ASTHMA SEVERITY

	Baseline	Week 2	Week 4	Week 8	Week 12	Wks 4-12
Tilade	2.47	2.00	1.76	1.83	1.86	1.81
Placebo	2.47	2.31	2.16	2.24	2.01	2.15
p value		0.007	0.008	0.006	0.415	0.009

At the end of the study, the clinician, patient and parent were asked to rate the effectiveness of the treatment as: very effective, moderately effective, slightly effective, no effect, or made condition worse, on a 1-5 scale in that order. Both Tilade and placebo received good scores on this scale and there was no significant difference between the two. The clinician rating gave 63% of Tilade patients versus 54% of placebo patients very or moderately effective ratings. For the patients, these high ratings were given to 71% for Tilade and 56% for placebo. Corresponding ratings from the parents were 73% for Tilade and 76% for placebo. These ratings numerically favored Tilade over placebo.

CONCLUSIONS ON EFFICACY

In this study, Tilade demonstrated superiority over placebo in asthmatic children age 6 to 12 years. On the primary analysis time period (weeks 3 to 12), Tilade clearly beat the placebo group with statistical significance on the primary endpoint - Worst Symptom score. The sponsor had argued in the protocol that it chose to use the Worst Symptom because there is a wider variance in the manifestation of asthma in children than in adults. The most predominant symptom identified at baseline should be more responsive to intervention (and thus likely to demonstrate a difference if one existed) than a total symptom score.

As it turned out, over 70% of the patients had daytime asthma symptom as their most troublesome symptom. Tilade beat placebo on this symptom and on cough as well, in the entire study population. The sponsor also carried out the traditional Summary Symptom Score analysis (combining daytime, nighttime and cough scores) in the efficacy population. This analysis also favored Tilade, with statistically significantly difference, over placebo. Remarkably, Tilade failed to win on nighttime asthma, a curious finding considering that a 'disease-modifying' therapy such as Tilade would be expected to improve overall asthma control, a key component of which is ability reduction in nocturnal asthma.

Results on secondary efficacy variables such as AM PEFR, FEV_1, physician scores etc., were spotty; Tilade beat placebo on some of these but not on others. Nonetheless, this study supports the overall efficacy of Tilade in a pediatric asthma population, aged 6 to 12 years.

4.4 SAFETY RESULTS

4.4.1 ADVERSE EVENTS (AE's)

Adverse event information were collected by questioning the patients at clinic visits. A total of 163 patients (80 on Tilade and 83 on placebo) were included in the safety analysis; one Tilade patient and 2 placebo patients who did not receive study treatment were excluded, out of the 166 randomized into the study. One hundred and twenty-two (122) patients reported at least one AE; 58 (or 73%) in the Tilade group and 64 (or 77%) on placebo. Table 4.4.1 below shows the major AE's recorded during the study. AE's were

selected for inclusion in this table (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on placebo or only occurred in one patient were excluded from this list. Unpleasant taste, pharyngitis, dyspepsia, fever and insomnia stand out as AE's that were more frequently associated with Tilade than with placebo. Bitter or unpleasant taste is a well known adverse effect of the Tilade drug substance. While pharyngitis and dyspepsia could be related to the inhalation product, fever and insomnia even though more frequent on active drug, are difficult to explain based on what is known about this drug.

Table 4.4.1 Occurrence of the AE's

ADVERSE EVENT	TILADE (n=80)	PLACEBO (n=83)
Headache	20%	19%
Pharyngitis	15	10
Sinusitis	10	8
Dyspepsia	11	6
Fever	11	5
Otitis Media	10	6
Rhinitis	9	6
Unpleasant Taste	8	2
Insomnia	4	0
Pruritus	3	0
Chest pain	3	0
Infection	3	0
Leg cramps	3	0

4.4.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

Nine patients dropped out of the study due to adverse events; 6 on Tilade and 3 on placebo. Table 4.4.2 below shows the AE's leading to withdrawal from the study for the 12 patients. None of the causes of withdrawal on Tilade appeared particularly unusual. No deaths were reported during the study.

TABLE 4.4.2 Adverse Event Withdrawals

	DURATION	SEVERITY	DAYS ON STUDY
TILADE			
Pneumonia	16 days	moderate	63
Light headedness/burning in throat	at each drug use	moderate / mild	4
Wheeze/cough	5 days	severe	57
Cough/SOB/nasal congestion	not stated	severe/moderate	27
Cough	9 days	severe	8
Asthma exacerbation/sinusitis/URI	1/7/7 days	moderate/severe	74
PLACEBO			
Sinus infection/URI	29 days	moderate	25
Acute bronchitis	10 days	moderate	55
Asthma exacerbation/URI	28 days	moderate	11

4.4.3 LABORATORY DATA

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and at the last study visit. Tests done included blood biochemistry, hematology and urinalysis. In the Tilade arm, one patient had a rise in SGPT from baseline value of 44 to 58 U/L at the end of the study. Alkaline phosphatase was also increased from 398 to 479 U/L. No clinical abnormalities were associated. A review of the LFTs in other patients showed that this was an isolated event. The SGPT normalized on repeat, although the alkaline phosphate remained elevated at 438 U/L. No systematic shifts were seen in the other lab parameters in the population studied.

CONCLUSIONS ON SAFETY

This study, carried out in the pediatric population, supports the safety profile for Tilade Nebulizer Solution. Even though the patients were quite young and much reliance was placed on parents reporting and recording AE's, the profile seen here for the active drug compares well with that seen in adult studies. Adverse events were fairly in line with what would be expected, with unpleasant taste perhaps the most striking side-effect. In general, the lab data showed no clinically significant abnormality. Overall, the safety of Tilade, based on the data in this study, is within acceptable limits.

5.0 STUDY CR 1409 (vol 1.53 et seq., data tables in vol 1.54 et seq)

RÉSUMÉ

This 'symptom reduction' trial was in 121 adult asthmatics with mild-moderate symptoms. Tilade was administered at 1 ampule (11 mg) four times daily. In this study, which had a similar design to CR 1408, Tilade failed to show a significant superiority over placebo on the main efficacy endpoints: summary symptom score, sleep difficulty and daytime asthma, as well as peak flow and FEV1 measurements. Although it failed on efficacy, the safety results are within the limits seen in other Tilade trials.

5.1 STUDY DESCRIPTION

This study in adult asthmatics had a protocol very similar to study CR 1408, except for some variations noted below. It was a double-blind, randomized, placebo-controlled, 16-week study (2-week run-in, 2-week baseline and 12-week treatment periods) of 0.5% Nedocromil Sodium (Tilade) Nebulizer Solution at doses of 11 mg (1 ampule) QID versus placebo, in asthmatic adults (age range 18-70 years). There were 5 study centers: Roger Bone, Chicago, IL; Leonard Hudson, Seattle, WA; Gail Shapiro, Seattle, WA; James Chauncey, Ann Arbor, MI; Robert Louden, Cincinnati, OH. The study was conducted from March 1988 to June 1989.

There was a 2-week run-in and then a 2-week baseline period, after which patients were randomized to receive either Tilade or placebo four times per day for a 12-week period. At study entry, patients were required to have FEV_1 greater than 40% predicted. Clinic visits occurred at study entry, and after 2,4,6,8 10 and 12 weeks of treatment. Patients recorded in their daily diary the AM and PM PEFR, daytime asthma severity, sleep difficulty due to asthma, daytime cough, and the use of study drug and concomitant medications (PRN bronchodilators and theophylline). Daytime asthma and cough were both scored on a scale of 0 to 4 for none; mild:symptoms (or cough) barely noticeable; moderate: symptoms noticeable but not bad enough to interfere with daily routine; severe:symptoms noticeable enough to interfere with daily routine; very severe: symptoms present most of the day and radically changed daily routine. Sleep difficulty due to asthma was scored on a 3-point scale: 0=slept well, no asthma; 1=woke once because of asthma; 2=woke more than once because of asthma. Other assessments during the study included PFTs, investigator rating of patient's severity of asthma on 0 to 4 scale (same scale as used by the patient for daytime symptom score), both at each 2-weekly visit. At the final visit (week 12), the patient and investigator rated the overall effectiveness of the treatment as 1=very effective, 2=moderately effective, 3=slightly effective, 4=no effect, or 5=made condition worse. Adverse event were recorded in the daily diary and also elicited by questioning during each of the clinic visits and recorded by the investigator in the CRF.

The protocol-defined period for analysis was the last 8 weeks of the trial: weeks 5 to 12. Binary variables were assessed using Fisher's exact test while a two-way main effects analysis of variance was used to assess overall treatment group comparison. In addition, both parametric and non-parametric analyses were carried out on the individual and summary symptom scores.

5.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total screened			147
Total Randomized	59	62	121
Completed	45	48	93
Total dropouts	14	14	28
Dropout due to non-compliance	4	-	
Dropout due to treatment failure	-	7	
Dropout due to adverse events	6	3	
Dropout due to intercurrent illness	1	-	
Dropout due to protocol violation	1	1	
Dropout on primary physician's request	1	-	
Dropout due to move outside trial area	1	1	
Dropout due to other reasons	-	2	
Efficacy Analysis population	53	58	111
Safety Analysis population (Intent-to-Treat)	59	62	121

Patient Characteristics

A total of 121 patients (59 on Tilade and 62 on placebo) were randomized to treatment out of 147 patients screened. There were 28 dropouts from the study, thus 93 of the 121 randomized patients completed the study. A total of 10 patients were excluded from the efficacy analysis due to various protocol violations. Thus there were 111 patients in the efficacy subset: 53 on Tilade, 58 on placebo. Of the 111 patients in the efficacy population, 72 were male and 39 were female. Age range for this efficacy population was 12-70 years, mean was 38.7 years for Tilade and 38.6 years for the placebo group. Mean baseline summary symptom score was 3.42 for Tilade and 3.59 for placebo, and baseline FEV_1 was 2.26 and 2.02 respectively (the difference in FEV_1 approached statistical significance, $p=0.076$).

The efficacy analysis consisted of the 111 patients discussed above while an intent-to-treat analysis was carried out for safety, including all 121 randomized patients.

5.3 EFFICACY RESULTS

The primary efficacy variable was the summary symptom score, i.e. the sum of the scores for sleep difficulty due to asthma AND daytime asthma severity. The primary time period for efficacy analysis was the last 8 weeks of the study: weeks 5 to 12.

Table 5.3A (extracted from vol 1.53, pg. 8-43-72; baseline data from pg 8-43-190 et seq) shows the mean data for the summary symptom score, and for sleep difficulty and daytime asthma scores. For each variable the mean is shown at baseline, averaged over the primary efficacy period (weeks 5 to 12) and over the entire study period.

On the primary efficacy endpoint over weeks 5-12, Tilade failed to beat placebo although the trend favored Tilade numerically. On the two scores making up the summary score, only on sleep difficulty did the difference between active and placebo approach statistical significance (p=0.08) in favor of Tilade. Although Tilade was numerically superior to placebo on daytime score, this too was not significantly different between the two arms. Overall therefore, Tilade failed to establish a statistically significant superiority over placebo on the diary symptom scores, individually and combined.

As shown in table 5.3B below, Tilade also failed to beat placebo on cough severity. However, the placebo group used significantly more concomitant medication (p=0.005), which may explain some (but perhaps not all) the improvement in symptom scores seen in that group compared to the active arm. Baseline use of concomitant medication was not different between the two groups.

Table 5.3A **Mean baseline and on-study data for the primary efficacy variable (summary symptom score), sleep difficulty and daytime asthma. LOCF, ANOVA analysis. (On-study means are adjusted for baseline only).**

		TILADE n=53	PLACEBO n=58	*p value*
Summary symptom score	Baseline*	3.42	3.59	0.211
	Weeks 5-12	2.38	2.67	0.152
Sleep difficulty	Baseline	1.21	1.11	0.358
	Weeks 5-12	0.84	0.93	0.080
Daytime asthma	Baseline	2.20	2.29	0.351
	Weeks 5-12	1.53	1.74	0.386

*Baseline values in this table and in table 5.3B are only for the efficacy subset and differ from the intent-to-treat baseline values.

Table 5.3B **Mean baseline and on-study data for cough severity and concomitant medication use. LOCF, ANOVA analysis. (On-study means are adjusted for baseline only).**

		TILADE n=53	PLACEBO n=58	p value
Cough Severity	Baseline	1.47	1.59	0.483
	Weeks 5-12	1.18	1.46	0.215
Concomitant Medication Use	Baseline	4.64	4.55	0.987
	Weeks 5-12	3.40	4.03	0.005

On two-weekly averages of the summary symptom score, Tilade also failed to beat placebo at all timepoints except at week 9-10 when the mean value of 2.30 for Tilade and 2.59 for placebo approached statistically significant difference (p=0.057). A similar picture is seen when Tilade is compared to placebo at 2-weekly time points on sleep difficulty, and daytime asthma severity.

5.3.1 SECONDARY EFFICACY VARIABLES: PEFR and FEV_1 measurements.

Patients measured and recorded their PEFR twice daily. Pulmonary Function Tests were recorded at each visit. As shown in table 5.3.1 below, Tilade failed to beat placebo on AM PEFR, PM PEFR and on FEV_1 during the primary analysis period, weeks 5-12. The trend nonetheless favored Tilade over placebo.

TABLE 5.3.1 PEFR and FEV_1

	TILADE (n=53)	PLACEBO (n=58)	*p value*
AM PEFR *(L/min)*			
Baseline	333.9	317.8	0.372
Week 5-12 average	346.3	328.3	0.120
PM PEFR *(L/min)*			
Baseline	361.6	349.5	0.503
Week 5-12 average	374.2	356.3	0.154
FEV_1 *(L)*			
Baseline	2.26	2.02	0.076
Week 5-12 average	2.22	2.21	0.390

At the end of the study, the clinician and patients were asked to rate the effectiveness of the treatment as:

very effective, moderately effective, slightly effective, no effect, or made condition worse, on a 1-5 scale in that order. Both Tilade and placebo received good scores on this scale and there was no significant difference between the two. The clinician rating gave 63% of Tilade patients versus 54% of placebo patients very or moderately effective ratings. Similar high ratings were given to 71% for Tilade and 56% for placebo by the patients. These ratings numerically favored Tilade over placebo.

CONCLUSIONS ON EFFICACY

In this study, Tilade failed to beat placebo on the major efficacy endpoints. The sponsor (and the review statistician- Barbara Bono) carried out various analysis of the data: parametric versus non-parametric, intent-to-treat versus evaluable, etc. At best, efficacy was patchy and unsustained on many of these analyses. Overall therefore, study CR 1409 is a failed trial.

5.4 SAFETY RESULTS

5.4.1 ADVERSE EVENTS (AE's)

Adverse event (AE) information were collected by questioning the patients at clinic visits (no direct recording of AE's in the diaries). A total of 121 patients (59 on Tilade and 62 on placebo) were included in the safety analysis. Seventy-two (72) patients reported at least one AE; 34 (or 58%) in the Tilade group and 38 (or 61%) on placebo. Table 5.4.1 below shows the major AE's recorded during the study. AE's were selected for inclusion in this table (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on placebo or only occurred in one patient were excluded from this list.

The overall AE profile emerging from this trial favors Tilade. Common adverse events usually associated with the drug (as seen in other trials) such as headache, URI and pharyngitis were more frequently associated with placebo in this particular trial. Increased sputum, bronchospasm and unpleasant taste were the main symptoms that appeared more frequent on Tilade than placebo.

Table 5.4.1 Occurrence of the AE's

ADVERSE EVENT	TILADE (n=59)	PLACEBO (n=62)
Headache	17%	23%
URI	12	19
Sputum increased	8	5
Sinusitis	7	5

...table continued next page

Table 5.4.1 Adverse Events cont'd.

ADVERSE EVENT	TILADE (n=59)	PLACEBO (n=62)
Bronchospasm aggravated	2	10
Dyspnea	5	5
Taste perversion	5	2
Diarrhea	5	2
Rhinitis	5	2
Pruritus	3	0
Anxiety	3	0
Bronchospasm	3	0
Hot flushes	3	0
Urticaria	2	1

5.4.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

Seventeen patients dropped out of the study due to adverse events; 7 on Tilade and 10 on placebo. Table 5.4.2 below shows the AE's leading to withdrawal from the study for the 17 patients. None of the causes of withdrawal on Tilade appeared particularly unusual. No deaths were reported during the study.

TABLE 5.4.2 Adverse Event Withdrawals

	DURATION	SEVERITY	DAYS ON STUDY
TILADE			
Wheezing/cough increased sputum/chest tightness	11 days	severe	41
Anxiety/insomnia/diarrhea hot flashes/chills	1-6 days	mild (except for insomnia: severe)	13
Headache/bad taste	1 hr with meds	mild/moderate	15
Wheezing/SOB	2 hrs	severe	26
Headache/irritability/drowsiness	6-7 days	moderate	8
Hip surgery	unknown	unknown	15
Light headedness/sleep disturbance /pounding heart	6 hours	moderate	1

TABLE 5.4.2 Adverse Event Withdrawals cont'd.

	DURATION	SEVERITY	DAYS ON STUDY
PLACEBO			
Increased asthma/cough/congestion	unknown	unknown	14
URI	unknown	unknown	69
Increased wheezing/SOB	unknown	unknown	40
Throat & lung irritation/congestion	1 hr after dose	moderate-severe	24
Acute asthma attack	5 days	severe	26
URI/influenza	7 days	moderate	17
Asthma attack	6 hours	moderate	9
Chest tightness	1 hr after dose	moderate	30
Asthma exacerbation/dyspnea /chest tightness	2 days	moderate-severe	4
Asthma attack/URI	1/8 days	severe/moderate	42

5.4.3 LABORATORY DATA

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and at the last study visit. Tests done included blood biochemistry, hematology and urinalysis. There were no significant changes on the lab measurements except on hematocrit which was statistically lower in the placebo group. The Tilade group changed from 45.09 g/dL at baseline to 45.13 at study completion, while the placebo group changed from 44.32 to 43.42 g/dL. Neither this change nor any of the minor changes in the individual lab data could be considered to be clinically significant.

CONCLUSIONS ON SAFETY

This study in adolescent and adult asthmatics (age 12 to 70 years) support the safety of Tilade in this population. Adverse event profile and laboratory data are all within acceptable limits, and comparable to those seen in the other pivotal trials.

6.0 STUDY CR 1691 (vol 1.59 et seq.)

RÉSUMÉ

This 'symptom reduction' study in 139 asthmatic patients aged 12 to 67 years failed to show efficacy for Tilade. In the trial, the drug was given at 1 ampule three times daily. On all the main efficacy variables, Tilade failed to beat placebo. Adverse event profile showed some mild exacerbation of airway-related symptoms but there were no significant dropout from the study and laboratory data were within acceptable limits.

6.1 STUDY DESCRIPTION

This study in adult asthmatics had a protocol almost identical to study CR 1409, except that Tilade was given three times daily rather than four times daily, as done in the other "Symptom Reduction" studies. It was a double-blind, randomized, placebo-controlled, 16-week study (2-week run-in, 2- week baseline and 12-week treatment periods) of 0.5% Nedocromil Sodium (Tilade) Nebulizer Solution at doses of 11 mg (1 ampule) TID versus placebo, in asthmatic adults (age range 18-70 years). There were 5 study centers: James Kemp, San Diego, CA; David Lefkowitz, Charlotte, NC; Barry Paull, Bryan, TX; Roger Menendez, El Paso, TX; Stephen Rennard, Omaha, NE. The study was conducted from Jan 1989 to April 1990.

There was a 2-week run-in and then a 2-week baseline period, after which patients were randomized to receive either Tilade or placebo four times per day for a 12-week period. At study entry patients were required to have FEV_1 greater than 40% predicted. Clinic visits occurred at study entry, and after 2,4,6,8 10 and 12 weeks of treatment. Patients recorded in daily diaries AM and PM PEFR, daytime asthma severity, sleep difficulty due to asthma, daytime cough, and the use of study drug and concomitant medications (PRN bronchodilators and theophylline). Daytime asthma and cough were both scored on a scale of 0 to 4 for none; mild:symptoms (or cough) barely noticeable; moderate: symptoms noticeable but not bad enough to interfere with daily routine; severe:symptoms noticeable enough to interfere with daily routine; very severe: symptoms present most of the day and radically changed daily routine. Sleep difficulty due to asthma was scored on a 3-point scale: 0=slept well, no asthma; 1=woke once because of asthma; 2=woke more than once because of asthma. Other assessments during the study included PFTs, investigator rating of patient's severity of asthma on 0 to 4 scale (same scale as used by the patient for daytime symptom score), both at each 2-weekly visit. At the final visit (week 12), the patient and investigator rated the overall effectiveness of the treatment as 1=very effective, 2=moderately effective, 3=slightly effective, 4=no effect, or 5=made condition worse. Adverse events were recorded in the daily diary and also elicited by questioning during each of the clinic visits and recorded by the investigator in the CRF.

The protocol-defined period for analysis was the last 8 weeks of the trial: weeks 5 to 12. Both a parametric and non-parametric analyses were carried out on the individual and summary symptom scores. The agency requested the parametric ANCOVA tests while the sponsor had specified the non-parametric analyses of the rank-transformed data in the protocol. Only the parametric data are discussed in this review.

6.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total screened			177
Total Randomized	68	71	139
Completed	64	56	120
Total dropouts	4	15	19
Dropout due to uncontrolled asthma	1	4	
Dropout due to intercurrent illness	1	1	
Dropout due to non-cooperation	2	8	
Dropout due to intolerance	-	2	
Efficacy Analysis population	67	71	138
Safety Analysis population (Intent-to-Treat)	68	71	139

Patient Characteristics

A total of 139 patients (68 on Tilade and 71 on placebo) were randomized to treatment out of 177 patients screened. There were 19 dropouts from the study, thus 120 of the 139 randomized patients completed the study. Only 1 patient (on Tilade) was excluded from the efficacy analysis due to protocol violation (using corticosteroid during the run-in). Thus there were 138 patients in the efficacy subset: 67 on Tilade, 71 on placebo. Of the 138 patients in the efficacy population, 91 were male and 47 were female. Age range for this efficacy population was 12-67 years, mean was 34.5 years for Tilade and 31.6 years for the placebo group. Mean baseline summary symptom score for Tilade was 2.26 and for placebo, 2.31. Mean baseline FEV_1 was 2.69 and 2.59 respectively.

6.3 EFFICACY RESULTS

The primary efficacy variable was the summary symptom score, i.e. the sum of the scores for sleep difficulty due to asthma AND daytime asthma severity. The primary time period for efficacy analysis was the last 8 weeks of the study: weeks 5 to 12. The individual symptom scores: sleep difficulty, daytime asthma and cough severity were all analyzed as secondary symptoms. Similarly PEFR, concomitant medication and FEV_1 were secondary variables. As shown in tables 6.3A, 6.3B and 6.3C below, Tilade, given at 1 ampule three times daily, failed to beat placebo on any of the 7 efficacy endpoints analyzed. This therefore is a failed study. Although the numerical trend appeared to favor Tilade on some of the endpoints, the placebo patients also showed a trend towards improvement on many of the variables.

Table 6.3A **Mean baseline and on-study data for the primary efficacy variable (summary symptom score), sleep difficulty and daytime asthma. LOCF, Parametric ANCOVA analysis. (On-study means are adjusted for baseline only).**

		TILADE n=67	PLACEBO n=71	*p value*
Summary symptom	Baseline*	2.26	2.31	0.71
	Weeks 5-12	1.91	2.07	0.17
Sleep difficulty	Baseline	1.01	1.16	0.17
	Weeks 5-12	0.88	1.00	0.09
Daytime asthma	Baseline	2.50	2.30	0.03
	Weeks 5-12	2.05	2.16	0.37

*Baseline values in this table and in table 6.3B & 6.3C are from vol 1.53, pg. 8-49-71. The on-study means are from page 8-49-42.

Table 6.3B **Mean baseline and on-study data for cough severity and concomitant medication use. LOCF, ANOVA analysis. (On-study means are adjusted for baseline only).**

		TILADE n=67	PLACEBO n=71	p value
Cough Severity	Baseline	1.54	1.32	0.13
	Weeks 5-12	1.54	1.69	0.57
Concomitant Medication Use	Baseline	4.40	4.44	0.98
	Weeks 5-12	3.95	4.05	0.98

TABLE 6.3C PEFR and FEV_1

	Tilade (n=67)	Placebo (n=71)	*p value*
AM PEFR *(L/min)*			
Baseline	386.1	374.2	0.72
Week 5-12 average	382.3	377.8	0.77
PM PEFR *(L/min)*			
Baseline	414.5	408.9	0.98
Week 5-12 average	412.9	406.4	0.38
FEV_1 *(L)*			
Baseline	2.69	2.59	0.68
Week 5-12 average	2.71	2.74	0.89

CONCLUSIONS ON EFFICACY

This is a failed study in which Tilade was unable to beat placebo on any of the efficacy endpoints. The reason for the failure is uncertain. Perhaps it is proof that Tilade is not efficacious in a three times daily dosing regime. However, study CR 1409 with an almost identical design but in which the active drug was given four times daily also failed to demonstrate efficacy. The value of this study is in the safety information which it provides.

6.4 SAFETY RESULTS

6.4.1 ADVERSE EVENTS (AE's)

Adverse event (AE) information were collected by questioning the patients at clinic visits and also through direct recording of AE's in the diaries by the patients. A total of 139 patients (68 on Tilade and 71 on placebo) were included in the safety analysis. One hundred and twenty-one (121) patients reported at least one AE; 50 (or 74%) in the Tilade group and 71 (or 61%) on placebo. Table 6.4.1 below shows the major AE's recorded during the study. AE's were selected for inclusion in this table (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on placebo or only occurred in one patient were excluded from this list.

There was an increased occurrence of upper and lower airway symptoms on Tilade compared to placebo. URI, coughing, bronchitis, increased sputum and rhinitis appeared more frequent on the active drug arm than on the placebo arm. The cause of this is uncertain. Although it may be speculated that some of the symptomatology may reflect 'treatment failure', failure to observe comparable events on placebo raises doubt that these AE's were due to the inability of Tilade to control the asthma symptoms. None of the other studies showed this distinct trend. Headache was also more frequent on Tilade as has been observed in some other trials.

Table 6.4.1 Occurrence of the AE's

ADVERSE EVENT	TILADE (n=59)	PLACEBO (n=62)
Headache	32%	17%
URI	28	17
Coughing	12	7
Bronchitis	12	3
Sputum Increased	9	3
Rhinitis	7	3
Nausea	6	3
Viral Infection	6	3
Vomiting	6	1
Dyspepsia	6	1
Pain	7	0
Earache	4	0
Chest pain	3	1
Fever	3	1
Dysphonia	1	1
Unpleasant taste	1	0
Bronchospasm	0	1
Dyspnea	0	1

6.4.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

Only 1 patient discontinued from the study for a reason remotely related to an adverse event. The 14 year old patient in the Tilade arm was dropped due to overdosing on theophylline. This was deemed to have been caused by an anxiety reaction and behavior disorder.

6.4.3 LABORATORY DATA

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and at the last study visit. Tests done included blood biochemistry, hematology and urinalysis. There were no significant changes on the lab measurements except on total plasma protein and globulin. These changes were mild and unlikely to be of any clinical significance.

CONCLUSIONS ON SAFETY

This study of Tilade given three times daily in adolescent and adult asthmatics (age 12 to 70 years), in general, support the safety of Tilade in this population. There was an unusual increase in adverse events related to the airway. However, data on dropout from the study and the laboratory measurements showed no unexpected findings.

7.0 STUDY CR 1978 (vol 1.70 et seq.)

RÉSUMÉ

This 'maintenance' study in 93 very mild asthmatic children aged 6 to 12 years in which Tilade was given at 11 mg TID for 24 weeks failed to show efficacy for Tilade on the primary variable: summary symptom score. Efficacy was also not demonstrated on the other variables, such as daytime symptoms, sleep difficulty, AM & PM PEFR and concomitant medication use. However, a post-hoc analysis of the percent symptom-free days showed Tilade to be superior to placebo at a statistically significant level. The adverse event profile was, in general, similar to those seen in the other trials except for a slight increase in the occurrence of chest pain on Tilade. Withdrawals due to adverse events as well as laboratory data were within acceptable limits.

7.1 STUDY DESCRIPTION

DESIGN: Double-blind, randomized, placebo-controlled, 7-center, 26-week study (24-week treatment period) of 0.5% Nedocromil Sodium (Tilade) Nebulizer Solution at doses of 11 mg (1 ampule) TID versus placebo, in asthmatic children (age 6 to 12 years).
INVESTIGATORS: Seven centers: Peter Konig, Columbia, MO; Howard Eigen, Indianapolis, IN; Mark Ellis, Orange, CA; Elliot Ellis, Jacksonville, FL; David Geller, St. Petersburg, FL; Gail Shapiro, Seattle, WA; Michael Welch, San Diego, CA.
POPULATION: Children age 6-12 years, with mild to moderate asthma and positive methacholine challenge on enrollment.
MATERIALS: Nedocromil (0.5% soln) in 2 mL ampules of 11 mg drug; and matching placebo. The drug or placebo was delivered through a Fisoneb Ultrasonic Nebulizer Device.
OBJECTIVE: 1) To assess whether Tilade can reduce the asthma symptoms that accompany symptomatic respiratory infections (SRI). 2) To assess whether Tilade can affect the increase in bronchial hyperreactivity that occurs secondary to symptomatic respiratory infections. Secondary objectives included assessment of the safety and efficacy of Tilade in children and whether the drug could reduce the frequency or duration of symptomatic respiratory infection.
RATIONALE: This trial aimed at studying children with asthma during a peak season for symptomatic respiratory infections. During each attack, degree of airway hyperreactivity is documented with methacholine challenge testing. The challenge test was also carried out at the beginning and at the end of the study.
CRITERIA: To be included in the study, patients had to have a documented diagnosis of chronic asthma with reversibility (15% ↑ in FEV_1). Pre-bronchodilator FEV_1 should be >40% predicted. Excluded were patients who had received oral or parenteral steroids for >14 days within the 3 months preceding the study; patients who had required iv, im or oral steroids within 4 weeks and inhaled steroids within 2 weeks of the study; or cromolyn within 1 month of the study.
CONCOMITANT MEDs: Inhaled beta agonist (Ventolin MDI) as needed for bronchospasm was allowed at the investigator's judgement. Patients on sustained-release theophylline had to stay on the same dose throughout the study. Cromolyn (all inhaled forms), systemic antihistamine, inhaled corticosteroid, chronic use of oral steroid and ipratropium were all disallowed.

CONDUCT: There was a 2-week baseline period after which patients were randomized to receive either Tilade or placebo three times per day for a 24-week period. Clinic visits occurred at study entry, 2 weeks after entry, at the start of the double-blind period and at 6, 12, 18 and 24 weeks. In addition, patients were also required to be brought to the hospital whenever there were symptoms of a respiratory infection. Also, clinic visits were scheduled for 3 and 6 weeks after the onset of a respiratory infection. Nasal smears (for microscopy) were carried out during these episodes in 6 out of the 7 centers. Nasopharyngeal viral cultures were carried out to establish the infecting organism.

Patients recorded in their daily diary the AM and PM PEFR. PFTs were measured at each visit. Methacholine challenge tests were done at the start and end of the study and also during episodes of symptomatic respiratory infection. The diagnosis of the latter condition (SRI) was made in the presence of two or more of the following: stuffy nose, runny nose, sneezing, throat discomfort, headaches, fever and malaise.
Patients recorded in their diary their daily scores on daytime asthma and sleep difficulty severity on the following scale. Daytime asthma was scored on a scale of 0 to 4 where 0=none; 1=symptoms barely noticeable; 2=symptoms noticeable but not bad enough to interfere with daily routine; 3=symptoms noticeable enough to interfere with daily routine; 4=symptoms present most of the day and radically changed daily routine. Sleep difficulty due to asthma was scored on a 3-point scale: 0=slept well, no asthma; 1=woke once because of asthma; 2=woke more than once because of asthma.

Cough was rated daily on the same 0-4 scale as daytime asthma score. At the final visit, patients, their parents and the clinician rated the effectiveness of the study treatment on a 6 point scale:1=very effective, 2=moderately effective, 3=slightly effective, 4=no effect, or 5=made condition worse.

Adverse events were elicited by questioning during each of the clinic visits and recorded by the investigator. Blood and urine samples for lab studies were collected at the start and end of the trial.

DATA ANALYSIS The protocol-defined primary efficacy variable was the summary symptom score derived by adding the scores on daytime asthma severity, and on sleep difficulty due to asthma. The protocol-defined period for analysis was the last 8 weeks of the trial: weeks 5 to 12. In an addendum to the study report, the sponsor proposed that because of the mild nature of the asthma in the population enrolled, a more sensitive endpoint would be the percent of symptom-free days. A *post-hoc* analysis of this variable was therefore carried out and included in the addendum. Ordinal response variables were compared between treatment groups using Wilcoxon rank-sum tests within clinics. Across clinics, treatment groups were compared using Mantel-Haenszel test on standardized ranks, this being the primary analysis. A parametric ANCOVA was also carried out at the request of agency statisticians.

7.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total screened			108
Total Randomized	48	45	93
Completed	39	36	75
Total dropouts	9	9	18
Dropout due to non-compliance	5	8	
Dropout due to intolerable symptoms	2	0	
Dropout due to treatment failure	1	0	
Dropout due to adverse event	1	1	
Efficacy Analysis population	48	45	93
Safety Analysis population (Intent-to-Treat)	48	45	93

Patient Characteristics

A total of 93 patients (48 on Tilade and 45 on placebo) were randomized to treatment out of 108 patients screened. There were 18 dropouts from the study (for reasons shown in above table), thus 75 of the 93 randomized patients completed the study. All the 93 patients who were randomized were included in the efficacy analysis. There were 58 males and 35 females. Age range for the population was 6-12 years; mean was 8.81 years for Tilade and 9.16 years for the placebo group. Mean baseline summary symptom score for Tilade was 1.17 and for placebo 1.29. Mean baseline PEFR was 254.5 and 263.9 l/min respectively. While there was no significant difference in these baseline parameters between the two groups, these figures, in children aged 6 to 12 years, show that their asthma was very mild. On the average, the patients in the study were completely free of daytime symptoms and sleep-difficulty due to asthma on 6 out of the 14 baseline days (42.9% for both Tilade and placebo patients).

7.3 EFFICACY RESULTS

This study was designed to assess the effect of Tilade given three times daily in children aged 6 to 12 years on the asthma symptoms and bronchial hyperreactivity associated with symptomatic respiratory infections (SRI). The primary efficacy variable as stated in the protocol was the summary symptom score, i.e. the sum of the scores for daytime asthma and sleep difficulty. The primary time period for efficacy analysis was entire treatment period, i.e. 24 weeks. The individual symptom scores: daytime asthma, sleep

difficulty, and cough severity were all analyzed as secondary symptoms. Similarly, AM & PM PEFR and concomitant albuterol use were secondary variables. A *post-hoc* analysis of percent of symptom-free days was also carried out and included in the addendum to the study report. In this section of the review, first the protocol-defined primary and secondary variables are presented. Then the *post-hoc* analysis is discussed.

As shown in tables 7.3A the patients recruited into the study had very mild disease even though the protocol aimed at mild-moderate patients (baseline FEV_1 was only required to be over 40% predicted). Mean baseline symptoms were around 1, on a 5-point scale; mean PEFR was also in the mild range: >250 l/min.

Over the 24-week treatment period, Tilade failed to beat placebo on the primary endpoint, summary symptom score, as well as on the individual scores: daytime asthma, sleep difficulty and cough. Only on the summary symptom did Tilade show a trend toward improvement, as did the placebo group. On the individual symptoms, the Tilade group appeared to have worsened, based on the mean values. Similarly, Tilade did not beat placebo on the peak flow recordings and on the amount of concomitant medication used. But in this case both AM and PM PEFR increased in the Tilade group while they declined in the placebo arm.

Table 7.3A **Mean baseline and on-study data for the primary efficacy variable (summary symptom score), daytime asthma, sleep difficulty and cough severity. (On-study means are adjusted for baseline).**

		TILADE n=48	PLACEBO n=45	*p value*
Summary symptom	Baseline*	1.17	1.29	0.576
	24-wk avg	1.12	1.22	0.708
Daytime Asthma	Baseline	0.90	0.81	0.689
	24-wk avg	0.96	0.90	0.293
Sleep Difficulty	Baseline	0.27	0.33	0.509
	24-wk avg	0.31	0.33	0.698
Cough Severity	Baseline	0.89	1.12	0.156
	24-wk avg	1.04	1.00	0.441

*Baseline values and on-study means in this table and in table 7.3B are from page 8-61-45

Table 7.3B **Mean baseline and on-study data for AM & PM PEFR and concomitant medication. (On-study means are adjusted for baseline only).**

		TILADE n=48	PLACEBO n=45	*p value*
AM PEFR	Baseline	254.5	263.9	0.505
	24-wk avg	269.1	261.1	0.620
PM PEFR	Baseline	267.8	282.0	0.285
	24-wk avg	278.1	273.1	0.324
Concomitant Albuterol Use	Baseline	1.94	1.47	0.101
	24-wk avg	1.64	2.08	0.148

7.3.1 SYMPTOMATIC RESPIRATORY INFECTIONS AND PERCENT SYMPTOM-FREE DAYS

As discussed earlier, the sponsor argued that, given the mildness of the asthma in this population, a more sensitive endpoint would be the percent symptom-free days over the 24-week treatment period. One of the expectations of the study was that Tilade would reduce the level of symptoms associated with symptomatic respiratory infections compared to placebo. An analysis was therefore carried out to look at the occurrence of SRI as well as the percent symptom-free days. A symptom-free day was one during which the patient had no daytime asthma symptom (i.e. score=0), no sleep difficulty (score=0) and did not use oral corticosteroid or any other disallowed asthma medication.

The same proportion of patients on Tilade and on placebo had SRI: 33 of the 48 (68.8%) of the patients on Tilade and 31 out of 45 (68.9%) placebo patients. Duration of SRI episodes was 9.1±0.8SEM days on Tilade and 11.2±1.2 days on placebo; p=0.258. Also, time to first SRI episode was not different between the two arms: mean 52 versus 46 days on treatment. However, as shown in table 7.3.1 below, there was a statistically significant difference favoring Tilade over placebo (p=0.025) when the percent of symptom-free days was compared over the entire 6-month treatment period. The difference was even more striking (p=0.009) when the two treatments were compared over the first 3-month period, as shown below.

Table 7.3.1 **Percent of Symptom-free days. Parametric analysis.**

%SYMPTOM-FREE DAYS	TILADE (n=47)	PLACEBO (n=45)	*p value*
Baseline	42.9	42.9	
Weeks 1-12	57.6	44.7	0.009
Weeks 1-24	58.2	46.4	0.025

Additional *post-hoc* analyses were carried out on the number of courses of prednisone given during the study, the changes in methacholine PD_{20} after episodes of SRI, and severity of asthma symptoms during SRI episodes. None of these analyses showed a significant difference between Tilade and placebo. For example, no difference was seen in the mean PD_{20} at week 24, Tilade versus placebo (2.05 vs 2.26, p=0.619); 3-weeks post-SRI (1.96 vs 1.59, p=0.820); and 6-weeks post-SRI (2.22 vs 1.72, p=0.808).

CONCLUSIONS ON EFFICACY

Tilade failed to beat placebo on any of the pre-specified efficacy endpoints at a statistically significant level. Little or no efficacy was shown on the subjective symptom scores. On the peak flow and concomitant albuterol use endpoints, Tilade was numerically superior to placebo but again no statistical superiority was demonstrated. A few possible reasons that might have contributed to these findings are: 1) the fact that the patients enrolled in the study had very mild disease and were therefore less likely to show a difference than a more severely ill population; 2) the sample size perhaps was small; 3) possibility that subjective symptoms are often difficult to elicit from children 6-12 year old since the investigators had to rely on the parent's or guardian's assessment. This study, as well as studies 2233 and 3003, was designated a 'maintenance study' in the Tilade development program and was expected to demonstrate that Tilade could prevent increases in symptoms (relative to placebo). By starting with patients who were almost asymptomatic it became almost impossible to distinguish between Tilade and placebo in their ability to achieve this objective.

As discussed in section 7.3.1 above, the sponsor made similar arguments to explain the failure of this study on the protocol-specified endpoints. They therefore computed, *post-hoc* the percent symptom-free days variable. Tilade beat placebo significantly on this new endpoint. While this 'win' came from a *post-hoc* analysis, comfort can be taken in the fact that in a follow-up study (CR 2233) in children age 2 to 5 years (see section 8.0 of this review), Tilade succeeded in beating placebo on percent symptom-free days analysis. And in that case, the analysis was pre-specified in the protocol.

Overall therefore, this study showed no efficacy based on protocol-defined endpoints, but favored Tilade on *post-hoc* analysis.

7.4 SAFETY RESULTS

7.4.1 ADVERSE EVENTS (AE's)

Adverse event (AE) information were collected by questioning the patients at clinic visits. All the 93 randomized patients (48 on Tilade and 45 on placebo) were included in the safety analysis. Seventy nine (79) patients reported at least one AE; 43 (or 90%) in the Tilade group and 36 (or 80%) on placebo. Table 7.4.1 below shows the major AE's recorded during the study. AE's were selected for inclusion in this table (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on placebo or only occurred in one patient were excluded from this list.

Upper respiratory infection (URI) which occurred more frequently on Tilade than placebo in other studies behaved differently in this case, with the placebo group having slightly more cases. The AE's that appeared more common on the active arm included aggravated bronchospasm, headache, running nose and unpleasant taste. Chest pain was a surprising member of this group, since it is difficult to explain why

Tilade by itself would produce this AE (except as a manifestation of bronchospasm). It is noteworthy that in the other pediatric study (study CR 1574 in 6-12 year old asthmatics) chest pain also occurred more frequently on Tilade (3%) than on placebo (0%). The other AE's reported during this study followed the pattern seen in other studies.

Table 7.4.1 Occurrence of the AE's

ADVERSE EVENT	TILADE (n=48)	PLACEBO (n=45)
URI	31%	40%
Bronchospasm	31	33
Aggravated bronchospasm	29	22
Headache	23	18
Nose running	10	4
Chest pain	8	0
Unpleasant taste	6	2
Conjunctivitis	4	0
Lymphadenopathy	4	0
Rash	2	0
Dysphonia	2	0
Abdominal pain	2	0

7.4.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

Only 2 patients discontinued from the study due to adverse events; one patient from each arm. The Tilade patient withdrew after 9 days on treatment due to headache. The placebo patient dropped out of the study due to unpleasant taste of the study medication.

7.4.3 LABORATORY DATA

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and at the last study visit. Tests done included blood biochemistry, hematology and urinalysis. There were no significant changes on the lab measurements except on serum potassium where the Tilade arm had slightly These changes were mild and unlikely to be of any clinical significance.

CONCLUSIONS ON SAFETY

This study of Tilade given three times daily in children (aged 6 to 12 years) with minimal asthma symptoms, in general, support the safety of Tilade in this population. Many of the reported AE's were similar to those seen in other trials, but chest pain was particularly notable in this study population.

8.0 STUDY CR 2233 (vol 1.77 et seq.)

RÉSUMÉ

In this study of 279 mild asthmatic children age 2 to 5 years Tilade was given at 1 ampule (11 mg) TID for 12 weeks in order to demonstrate that the drug could minimize the likelihood of asthma symptoms in a so-called labile asthmatic population. Tilade showed a statistically significant superiority over placebo on the percent of symptom-free days, the protocol-defined primary variable. Tilade also beat placebo on some of the other efficacy endpoints such as summary symptom score, daytime asthma and cough. Safety profile for the drug from this study was within the expected range. This study, in the youngest population for which the drug would be labeled for, therefore supports the efficacy (as defined) and safety of Tilade Nebulizer Solution.

8.1 STUDY DESCRIPTION

This study in asthmatic children aged 2 to 4 years was similar in design to study CR 1978. It is the second of the 'maintenance studies' designed to show the benefit of Tilade in minimizing the likelihood of asthma symptoms in a so-called labile asthmatic population. Very mild asthmatics were enrolled during a particular time of the year - September 1991 to February 1992 in cohorts. To be included in the study, patients were required to have a history of acute exacerbations of asthma during the same time-frame (Sept to March) in the preceding year. The objective of the study was to determine the efficacy and safety of Tilade given as 1 ampule (11 mg) three times daily over a 12 week period. The efficacy was to be demonstrated by the ability of Tilade compared to placebo to maintain patients symptom-free despite the anticipated exposure to stimuli such as cold air, allergen and viral challenges during the study period.

As in study CR 1978, patients were not required to have any predefined level of symptoms at entry. However, patients who were completely symptom-free or nearly so during the baseline period were excluded from the study. Other inclusion criteria were as in study CR 1978. In addition, patients were required to have had at least 2 exacerbations of asthma during the Sept 1990 to March 1991 time-frame. The exacerbation must have required hospitalization, emergency room care, or physician contact consisting of acute medication or short course of oral steroids.

The study was a double-blind, randomized, placebo-controlled, 15-center trial. Following 2-week baseline, patients were randomized to receive either Tilade 1 ampule TID or placebo, for a 12 week period. Patients were seen in the clinic every 2 weeks throughout the study. Parents were required to keep daily diary of the asthma symptom level, activity level, the use of study drug and concomitant medication, and the occurrence of respiratory infection symptoms. Daytime asthma and cough were rated on the same 0-4 scale as in previous pivotal trials. Sleep difficulty (usually rated on a 0 to 2 scale) was rated on a 5-point scale in this study as follows: 0=slept well, no cough or wheeze; 1=cough or wheeze, did not wake up; 2=woke once because of cough or wheeze but went back to sleep; 3=woke 2 or more times but went back to sleep; 4=woke due to cough or wheeze and needed medication. Concomitant medications were recorded by name in the daily diary. Activity level of the child was assessed daily on a visual analogue scale of a 100 mm line with the left end marked 'not as playful as usual' and the right end 'more playful than usual'. Parents were asked to record in the diary the child's respiratory rate at bedtime each day.

Finally, the investigator and parent rated the effectiveness of the study treatment on the usual 1 to 5 scale: 1=very effective and 5=made condition worse.

Primary efficacy variable was the percentage of days over the 12-week period during which the patient had no daytime asthma symptom, sleep difficulty or any use of oral steroid or other disallowed asthma medications. Other efficacy assessments described above (symptom scores, concomitant medication use, activity level etc.) were analyzed as secondary efficacy variables. The assessment of symptom scores and of concomitant medication use focused primarily on weeks 5 to 12. A non-parametric analysis of covariance of ranks was the protocol-specified primary analysis. However, parametric analysis of the original data with baseline as co-variate was also presented on request by the Division. Also analyses were carried out on the efficacy population and the intent-to-treat group. Adverse events were elicited by questioning during each of the clinic visits and recorded by the investigator. Blood and urine samples for lab studies were collected at the start and end of the trial.

8.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total screened			324
Total Randomized	138	141	279
Completed	124	126	250
Total dropouts	14	15	29
Dropout due to non-compliance	3	6	
Dropout due to loss to follow-up	6	2	
Dropout due to intercurrent illness	2	2	
Dropout due to therapeutic failure	-	2	
Dropout due to adverse event	1	1	
Dropout due to AE and non-compliance	1	-	
Dropout due to URI during baseline	-	1	
Dropout for other reasons	1	1	
Efficacy Analysis population	132	137	269
Safety Analysis population (Intent-to-Treat)	136	140	276

Patient Characteristics

A total of 279 patients (138 on Tilade and 141 on placebo) were randomized to treatment out of 324 patients screened. There were 29 dropouts from the study (for reasons shown in above table), thus 250 of the 279 randomized patients completed the study. Two hundred and seventy-six of the 279 patients who were randomized were included in the safety analysis; three patients (2 on Tilade, 1 on placebo) who never received study medication before dropping out of the study were excluded. The efficacy analysis consisted of 269 patients (data for 10 patients - 4 Tilade, 6 placebo - were excluded due to lack of baseline data on some of the parameters, mostly respiratory rate in the majority of the 10 patients [info from appendix C3, vol 1.92, pg.8-82-53]).

The efficacy population (n=269) consisted of 176 (65.4%) male and 93 (34.6%) female Age range was 1.9 to 5 years; mean was 3.47 years for Tilade and 3.49 years for the placebo group.

Mean baseline summary symptom score (sum of daytime, sleep difficulty and cough) for Tilade was 3.16 and for placebo 2.87. Baseline percent symptom-free days (days when daytime and sleep difficulty scores were zero) were 30.9 % and 37.3% for Tilade and placebo respectively. These latter numbers which were close to being significantly different (p=0.08) suggest that the patients had mild disease as they did not have any symptoms for about one third of the baseline period.

8.3 EFFICACY RESULTS

This study was designed to assess the ability of Tilade given three times daily in children aged 2 to 5 years to maintain the patients symptom-free during the 12-week treatment period. The primary efficacy variable as stated in the protocol was the percent symptom-free days during the 12-week study period. The symptom scores, use of beta agonist, asthma scores during URI, and the investigator's and parent's assessments were analyzed as secondary variables.

One or more clinically-confirmed URI were seen in 71% of the Tilade patients and 77% of the placebo patients. Thirty nine (39) Tilade patients required prednisone treatment for asthma exacerbation during URI while 50 placebo patients needed prednisone intervention. A total of 57 courses of prednisone was given in the Tilade group compared to 82 courses in the placebo patients, although the mean number of days on prednisone was comparable between the two groups: 9.65 versus 10.16 days.

Table 8.3A shows the result of the analysis of the primary efficacy variable, the percent symptom-free days. Both groups had more symptom-free days during the treatment period compared to baseline. However, the change from baseline was much higher for the Tilade group compared to the placebo group, producing a statistically significant change in favor of Tilade over placebo. The sponsor also carried out an analysis combining the percent symptom-free days with the amount of beta agonist use in order to see if either group benefitted from using more rescue therapy. This analysis also favored Tilade with 15.8% increase from baseline on this hybrid variable compared to 6.8% on placebo, p=0.027. Tilade appeared to have reduced occurrence of symptoms while the patients were using comparable amount of rescue beta agonists (0.21 vs 0.20 times/day, respectively).

Table 8.3A Mean baseline and on-study data for the primary efficacy variable (percent symptom-free days)

Symptom-free days	TILADE (n=132)	PLACEBO (n=137)	*p value*
% of baseline period	30.9	37.3	
% of treatment period	47.1	42.1	
change from baseline (%)	16.3	4.7	0.006

8.3.1 ADDITIONAL SECONDARY VARIABLES: Symptom scores etc.

As shown in table 8.3.1A below, Tilade was superior to placebo at a statistically significant level on a number of the secondary endpoints. For example, Tilade beat placebo on daytime symptoms, cough and on the summary symptom score (which in this case combines daytime symptom, sleep difficulty and cough, scale 0-12). Although Tilade did not beat placebo on the concomitant use of beta agonists, the trend was in the right direction with a 0.17 times/day reduction from baseline on Tilade versus 0.05 on placebo.

Table 8.3.1A. Mean baseline and on-study data for Daytime Symptom Score, Sleep Difficulty, Cough, Summary symptom, use of beta agonists. (On-study means are adjusted for baseline only).

		TILADE n=132	PLACEBO n=137	*p value*
Daytime Symptom	Baseline	0.92	0.90	
	Wk 5-12	0.63	0.83	0.040
Sleep Difficulty	Baseline	0.97	0.80	
	Wk 5-12	0.67	0.80	0.204
Cough	Baseline	1.27	1.17	
	Wk 5-12	0.94	1.13	0.009
Summary Symptom	Baseline	3.16	2.87	
	Wk 5-12	2.24	2.76	0.014

Concomitant β_2-Agonists (times/day)	Baseline	0.71	0.67	
	Placebo	0.52	0.63	0.271

As shown in table 8.3.1B below, there was no significant change from baseline on the activity level (assessed on a visual analogue 0-100 scale), and on respiratory rate (/min) in both arms of the study. The difference between the Tilade and placebo groups was not significant on either of these two variables.

Table 8.3.1B. Baseline and Mean Values of Activity Level and Respiratory Rate

		TILADE (n=132)	PLACEBO (n=137)	*p value*
Activity Level	Baseline	50.0	48.6	
	Wk 5-12	50.7	50.4	0.458
Bedtime Resp Rate	Baseline	22.3	22.3	
	Wk 5-12	22.1	21.9	0.688

CONCLUSIONS ON EFFICACY

This study set out to prove that Tilade could maintain patients symptom-free for a longer time compared to placebo when given three times daily in very young children, aged 2 to 4 years. The study ended up enrolling children up to age 5 years. Tilade clearly showed efficacy over placebo on the primary endpoint, percent symptom-free days. This was achieved without the Tilade patients using more rescue therapy. Tilade was also superior to placebo on a few secondary endpoints e.g summary symptom scores, daytime symptom and cough although it failed to 'win' on others such as activity level and respiratory rate. Overall, this study supports the efficacy of Tilade in mild asthmatics aged 2 to 5 years

8.4 SAFETY RESULTS

8.4.1 ADVERSE EVENTS (AE's)

Adverse event (AE) information were collected by questioning the parents at clinic visits. Two hundred and seventy-six (276) of the randomized patients (136 on Tilade and 140 on placebo) were included in the safety analysis. Two hundred and fifty-nine (259) patients reported at least one AE; 130 (or 96%) in the Tilade group and 129 (or 92%) on placebo. Table 8.4.1 below shows the major AE's recorded during the study. AE's were selected for inclusion in this table (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on

placebo or only occurred in one patient were excluded from this list.

Upper respiratory infection (URI) occurred in similar proportion in the two study arms. A few other infection-related AE's appeared more common on Tilade than placebo: otitis media, influenza-like symptoms and herpes zoster. Given the marginal difference between the active drug and placebo on some of these AE's however, causality appears unlikely. Overall, the AE profile is not too dissimilar to that seen in the other studies including the adult trials.

Table 8.4.1 Occurrence of the AE's

ADVERSE EVENT	TILADE (n=136)	PLACEBO (n=140)
URI	69%	70%
Rhinitis	34	27
Fever	25	22
Otitis Media	13	9
Influenza-like symptoms	12	7
Headache	8	10
Bronchospasm aggravated	9	9
Diarrhea	10	4
Herpes Zoster	6	2
Bacterial Infection	5	1
Unpleasant taste	4	1
Increased sputum	1	0

8.4.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

Only 2 patients were listed as having discontinued from the study purely due to adverse events. However, a number of discontinuations were due in part to an adverse event. Four Tilade patients and 5 placebo patients were in this group of those who wholly or partially withdrew from the trial. Reasons for withdrawal were similar to those seen in other trials: asthma exacerbation, URI, otitis media or sinusitis.

8.4.3 LABORATORY DATA

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and

at the last study visit. Tests done included blood biochemistry, hematology and urinalysis. There were no significant changes on the lab measurements except on red cell distribution. Although the difference achieved statistical significance (12.95 vs 13.19 % counter argument), this change was mild and unlikely to be of any clinical significance.

CONCLUSIONS ON SAFETY

This study of Tilade given three times daily in children (aged 2 to 5 years) with mild asthma symptoms supports the safety of Tilade in this population. Many of the reported AE's were similar to those seen in other trials.

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9.0 STUDY CR 3003 (vol 1.94 et seq.)

RÉSUMÉ

This study of the efficacy of Tilade in maintaining mild asthmatics symptom-free was carried out in 293 asthmatics age 5 to 12 years who received the drug or placebo at 1 ampule (11 mg) three times daily over 12 weeks. On the primary efficacy variable, the percentage of symptom-free days on treatment, Tilade showed a numerical advantage over placebo, but was not statistically superior. There was also a numerically greater improvement on symptom scores - daytime, sleep difficulty and cough - and on AM PEFR on Tilade compared to placebo. But none of these comparisons achieved statistical significance. On efficacy evaluation therefore, this was a failed study. Safety profile of the drug was within the limits seen in other studies in that there were no unusual events.

9.1 STUDY DESCRIPTION

This study in asthmatic children aged 5 to 12 years was identical in design to study CR 2233. It is the third of the 'maintenance studies' designed to show the benefit of Tilade in minimizing the likelihood of asthma symptoms in a so-called labile asthmatic population. Mild asthmatics were enrolled during a particular time of the year - August 1992 to March 1993 in cohorts. The objective of the study was to determine the efficacy and safety of Tilade given as 1 ampule (11 mg) three times daily over a 12 week period. The efficacy was to be demonstrated by the ability of Tilade compared to placebo to maintain patients symptom-free despite the anticipated exposure to stimuli such as cold air, allergen and viral challenges during the study period.

As in study CR 2233, patients were not required to have any predefined level of symptoms at entry. However, patients who were completely symptom-free or nearly so during the baseline period were excluded from the study. Patients were required to be only on PRN beta agonists at study entry. Other inclusion criteria were as in study CR 2233 and CR 1978.

The study was a double-blind, randomized, placebo-controlled, 13-center trial. Following 2-week baseline, patients were randomized to receive either Tilade 1 ampule TID or placebo, for a 12-week period. In this study, the drug was delivered with a power-operated compressor/nebulizer. Patients were seen in the clinic every 2 weeks throughout the study. Parents were required to keep a daily diary of asthma symptom level, activity level, the use of study drug and concomitant medication, and the occurrence of respiratory infection symptoms. Daytime asthma and cough were rated on the same 0-4 scale as in previous pivotal trials. Sleep difficulty (usually rated on a 0 to 2 scale) was rated on a 5-point scale in this study as follows: 0=slept well, no cough or wheeze; 1=cough or wheeze, did not wake up; 2=woke once because of cough or wheeze but went back to sleep; 3=woke two or more times but went back to sleep; 4=woke due to cough or wheeze and needed medication. Concomitant medications were recorded by name in the daily diary. Activity level of the child was assessed daily on a 0 to 4 scale as follows:

0= patient was able to run/play much better today compared to before the study
1= patient was able to run/play a little better today...
2= patient was able to run/play the same today...
3= patient was somewhat limited in his ability to run/play today...
4= patient was unable to run/play today because of asthma

Parents were asked to record in the diary the child's respiratory rate at bedtime each day. Patients recorded the morning and evening PEFR. And finally, the investigator and parent rated the effectiveness of the study treatment on the usual 1 to 5 scale: 1=very effective and 5=made condition worse.

The primary efficacy variable was the percentage of days over the 12-week period during which the patient had no daytime asthma symptom, sleep difficulty or any use of oral steroid or other disallowed asthma medications. Other efficacy assessments described above (symptom scores, concomitant medication use, activity level etc.) were analyzed as secondary efficacy variables. The assessment of symptom scores and of concomitant medication use focused primarily on weeks 5 to 12. A non-parametric analysis of covariance of ranks was the protocol-specified primary analysis. However, parametric analysis of the original data with baseline as co-variate was also presented on request by the Division. Also, analyses were carried out on the efficacy population and the intent-to-treat group. Adverse events were elicited by questioning during each of the clinic visits and recorded by the investigator. Blood and urine samples were collected at the start and end of the trial for lab studies.

9.2 PATIENT DISPOSITION

	TILADE	PLACEBO	TOTAL
Total Screened			321
Total Randomized	148	145	293
Completed	134	129	263
Total dropouts	14	16	30
Dropout due to non-compliance	5	3	
Dropout due to loss to follow-up	5	3	
Dropout due to intercurrent illness	-	1	
Dropout due to therapeutic failure	3	4	
Dropout due to adverse event	1	4	
Dropout due to withdrawal of consent	-	1	
Efficacy Analysis population	147	144	291
Safety Analysis population (Intent-to-Treat)	148	144	292

Patient Characteristics

A total of 293 patients (148 on Tilade and 145 on placebo) were randomized to treatment out of 321 patients screened. There were 30 dropouts from the study (for reasons shown in above table), thus 263 of the 293 randomized patients completed the study. The efficacy analysis consisted of 291 patients including 166 (57%) male and 125 (43%) female. The two randomized patients who were excluded from the efficacy analysis were one placebo patient who was lost to follow-up immediately after randomization and one Tilade patient who received only 2 doses before stopping treatment. Age range for the efficacy population was 5.0 to 11.9 years; mean was 8.5 years for Tilade and 8.6 years for the placebo group. A total of 292 patients were included in the safety analysis; only the placebo patient who did not receive any study drug was excluded.

Mean baseline summary symptom score (sum of daytime, sleep difficulty and cough) for Tilade was 1.79 and for placebo 1.92. These figures, being on a 0-12 (combined) scale really confirmed that the patients had very mild asthma symptoms indeed. Baseline percent symptom-free days (days when daytime and sleep difficulty scores were zero) were 44.1% and 42.9% for Tilade and placebo respectively; further supporting the extreme mildness of their asthma at study onset.

9.3 EFFICACY RESULTS

This study was designed to assess the ability of Tilade given three times daily in children aged 5 to 12 years to maintain the patients symptom-free during the 12-week treatment period. The primary efficacy variable as stated in the protocol was the percent symptom-free days during the 12-week study period. The symptom scores, use of beta agonist rescue, asthma scores during URI, and the investigator's and parent's assessments were analyzed as secondary variables.

Thirty-four (34) Tilade patients (or 23.1%) required prednisone treatment for asthma exacerbation (mostly during URI) while 25 placebo patients (or 17.4%) needed prednisone intervention. The mean number of days on prednisone was comparable between the two groups: 7.6 versus 7.0 days.

Table 9.3A shows the result of the analysis of the primary efficacy variable, the percent symptom-free days. Both groups had more symptom-free days during the treatment period compared to baseline. However, the change from baseline was only marginally higher for the Tilade group compared to the placebo group, and no statistically significant difference was shown. The use of beta agonists on symptom-free days was similar between the two groups: 0.12 versus 0.17 times/day for Tilade and placebo, respectively.

Table 9.3A Mean baseline and on-study data for the primary efficacy variable (percent symptom free days)

Symptom-free days	TILADE (n=147)	PLACEBO (n=144)	*p value*
% during baseline period	44.1	42.9	
% during treatment period	53.8	50.9	
– change from baseline (%)	9.7	8.0	0.495

9.3.1 ADDITIONAL SECONDARY VARIABLES: Symptom scores etc.

As shown in table 9.3.1A below, Tilade did not beat placebo on any of the asthma symptom scores, either individually or on the combined summary variable. For Tilade, some of the endpoints showed a general trend in the right direction. However, the difference from placebo was small.

Table 9.3.1A. Mean baseline and on-study data for Daytime Symptom Score, Sleep Difficulty, Cough, Summary symptom, use of beta agonists. (On-study means are adjusted for baseline only).

		TILADE n=147	PLACEBO n=144	*p value*
Daytime Symptom	Baseline	0.67	0.74	
	Wk 5-12	0.54	0.66	0.936
Sleep Difficulty	Baseline	0.41	0.44	
	Wk 5-12	0.38	0.55	0.324
Cough	Baseline	0.71	0.75	
	Wk 5-12	0.62	0.73	0.284
Summary Symptom	Baseline	1.79	1.92	
	Wk 5-12	1.54	1.93	0.439
Use of β_2 Agonists (times/day)	Baseline	0.47	0.41	
	Placebo	0.54	0.55	0.309

As shown in table 9.3.1B below, there was no significant difference between Tilade and placebo on the activity level (assessed on a 0 to 4 scale), and on morning peak flow measurement although Tilade showed slight numerical advantage over placebo on both variables.

Table 9.3.1B. Baseline and Mean Values of Activity Level and AM PEFR.

		TILADE (n=132)	PLACEBO (n=137)	*p value*
Activity Level	Baseline	50.0	48.6	
	Wk 5-12	50.7	50.4	0.458
AM PEFR	Baseline	229.4	238.6	
	Wk 5-12	243.8	245.0	0.574

CONCLUSIONS ON EFFICACY

This study set out to prove that Tilade could maintain patients symptom-free for a longer time compared to placebo when given three times daily in children aged 5 to 12 years with very mild disease. The analysis of the efficacy data failed to support this claim at a statistically significant level, although the trend on many of the endpoints favored Tilade numerically. The cause of the failure is uncertain, but as in study CR 1978, perhaps the patients were too mild to distinguish between the two treatments.

9.4 SAFETY RESULTS

9.4.1 Adverse Events (AE's)

Adverse event (AE) information were collected by questioning the parents of the children at clinic visits. Two hundred and ninety-two (292) of the randomized patients (148 on Tilade and 144 on placebo) were included in the safety analysis. Two hundred and fifty-seven (257) patients reported at least one AE; 129 (or 87%) in the Tilade group and 128 (or 89%) on placebo. Table 9.4.1 below shows the major AE's recorded during the study. AE's were selected for inclusion in this table (by this reviewer) based on clinical relevance and occurrence in the Tilade arm relative to placebo. A number of AE's which occurred more frequently on placebo or only occurred in one patient were excluded from this list.

Upper respiratory infection (URI) occurred in similar proportions in the two study arms. GI-related adverse events: nausea and vomiting appear slightly more noticeable on Tilade than on placebo. Unpleasant taste followed the same pattern as has been seen on other studies: greater association with the active drug than placebo. Overall, the AE profile is not too dissimilar to that seen in the other controlled trials including the adult trials.

Table 9.4.1 Occurrence of the AE's

Adverse Event	TILADE (n=148)	PLACEBO (n=144)
URI	30%	31%
Bronchospasm	33	27
Headache	23	33
Fever	19	17
Vomiting	9	3
Nausea	8	3
Unpleasant taste	7	3
Influenza-like symptoms	6	2
Bronchitis	3	3
Chest pain	5	1
Diarrhea	3	1
Dizziness	3	1
Abdominal pain	3	0.7
Dry mouth	2	0

9.4.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

A total of 9 patients dropped out of the study partly or wholly due to adverse events. Two were on active treatment and 7 on placebo. The two Tilade patients included one 8 year old who discontinued on day 22 due to upper respiratory infection and 'status asthmaticus'. The other Tilade patient, a 10 year old female dropped out due to unpleasant taste on the drug. Neither of these events appeared unexpected.

9.4.3 LABORATORY DATA

Laboratory analyses were carried out on blood and urine samples collected during the baseline period and at the last study visit. Tests done included blood biochemistry, hematology and urinalysis. There were no clinically significant changes on the lab measurements.

CONCLUSIONS ON SAFETY

This study of Tilade given three times daily in children (age 5 to 12 years) with mild asthma symptoms supports the safety of Tilade in this population. Many of the reported AE's were similar to those seen in other trials.

10.0 INTEGRATED SAFETY SUMMARY (vols 1.120)

RÉSUMÉ

This integrated safety review was based primarily on the patients enrolled in 14 US and non-US 12-24 month, placebo-controlled trials and two US open-label, 52 week studies. In these 16 studies, a total of 1076 patients received Tilade Nebulizer solution in BID, TID or QID dosing while 933 received placebo. Adverse events were few on Tilade, with minimal differences between the active drug and placebo. The frequency of typical respiratory events such as pharyngitis, URI and bronchitis was not different between Tilade and placebo. Even headache which in some individual study reports appeared more frequent on Tilade than on placebo did not stand out in the pooled data, although taste perversion was the main event that appeared predominantly on Tilade and only rarely in the placebo group. This was true in the overall assessment of adverse event reports as well as in the review of dropouts due to adverse events. The taste problem raises concern about the validity of blinding during the study, and potential patient compliance problems during use. There was only one death in the database: a 48 year old Tilade-treated female in a non-US trial who was said to have had myocardial infarction. In general, lab measurements did not show any significant abnormality on Tilade. A few statistically significant lab changes recorded have little or no clinical significance. Overall, a satisfactory safety profile for Tilade.

APPROACH TO REVIEW

This review is based on the ISS submitted by the sponsor. This ISS review is organized as follows. Patient exposure and extent of safety database, overall adverse events etc. each makes up a section (10.1, 10.2 etc.). In order to avoid repetitions and reproduction of lengthy tables from the study report, this reviewer made percentage cut-offs on some AE listing after reviewing the entire data and being satisfied that no AE of importance would be excluded with such a procedure. Where outliers occurred, they are discussed, but in most cases attention is focussed on common AE's and those traditionally associated with nedocromil such as unpleasant taste or lack of effect. CRFs were reviewed for the one death reported and for adverse event dropouts.

10.1 PATIENT EXPOSURE AND EXTENT OF SAFETY DATABASE

10.1.1 PATIENT EXPOSURE & DURATION OF EXPOSURE

A total of 16 therapeutic studies were carried out with Tilade Nebulizer Solution: Fourteen were double-blind, placebo-controlled studies while two were long-term open-label studies. Of the 14 controlled trials, 8 were carried out in the United States and were discussed in sections 2.0 to 9.0 of this review, while 6 were European studies. Seven of the 14 controlled trials were QID trials, 6 were TID and 1 was a BID trial.

A total of 1,076 patients received Tilade in the 16 therapeutic trials described above. In addition, 493 subjects (mostly healthy volunteers) received various concentrations of Tilade in biopharm and bronchial challenge studies, with 472 receiving single doses and 21 receiving QID for 2 weeks. The 1076 patients in the 16 trials formed the core of the safety database, and most of the discussion in this review relates to them.

Of the 1076 patients in the 16 trials, 1051 (97.6%) received Tilade for at least 2 weeks; 966 were treated for at least 8 weeks and 918 for 12 weeks. Two hundred and seventy-one were treated for at least 24 weeks and 207 for 40 weeks. The maximum time of exposure was 52 weeks which included 99 patients. As shown in table 10.1.1 below, the largest group of patients (647) received Tilade for a range of 12-23 weeks.

Table 10.1.1 Exposure by weeks for Tilade only (placebo data not included)

Duration of Exposure(wks)	US Studies QID	US Studies TID	Non-US, QID	Non-US TID	Non-US BID	US long-term*	Total**
<1	6	2	12	1	1	3	22
2-7	26	25	7	7	6	14	71
8-11	6	6	28	1	2	5	43
12-23	255	328	54	90	34	23	761
24-39	0	39	0	0	0	25	39
40-52	0	0	0	0	0	207	0
TOTAL	293	400	101	99	43	277	936

* this open-label data of 1 year duration included 1 TID and 1 QID study. Patients were rolled over from 12-week studies.
** this total includes only the controlled studies

10.1.2 EXPOSURE BY DOSE

As shown in table 10.1.1 above, two main dosing regimen of the Tilade Nebulizer solution 0.5% were studied, i.e. QID and TID. A small number of patients received BID regimen (n=43 or 4% of the database) in a non-US study. In the total database, more patients (56%) received the TID dosing compared to the QID dosing (43%).

10.1.3 DEMOGRAPHICS

The indication being sought for Tilade Nebulizer Solution covers age 2 to adults. Of the 1076 patients who received Tilade in the controlled trials, 367 or 34% were aged 5 years or younger, 259 or 24% were between 6 and 11 years old, and 432 or 40% were between 12 and 65 years old. Only 18 or 2% were 66 years or older. Further, in the open-label, 52-week trials, there were 202 children aged 5 or younger, with 77 completing the entire 52 weeks. In the uncontrolled trials, 22 out of the 70 enrolled adults completed the 52 weeks duration. Thus the database for Tilade consisted of 99 patients (77 plus 22) who received the drug for 52 weeks. Table 10.1.3 below shows the distribution of the safety database patients by age range.

Of the 1076 patients in the Tilade trials, 650 or 60% were males and 426 (40%) were females. The proportion is also preserved in the US controlled trials where 440 out of 693 (63%) were males and 253 (37%) were females. In the non-US controlled trials there were equal number of males and females: 122 versus 121, among the 243 patients enrolled. The US long term open-label studies had 176 males (64%) and 101 females (36%).

The sponsor did not provide information on the racial breakdown of the patients in the safety database.

Table 10.1.3. Demographics from the US and Non-US trials

Ages (years)	US controlled trials	Non-US controlled trials	US long-term open-label trials	All US studies	All controlled studies
≤5	155	109	202	258	264
6 to 11	240	19	0	240	259
12 to 65	293	103	70	329	396
≥66	5	12	5	6	17

10.2 OVERALL ADVERSE EVENTS

The sponsor analyzed the adverse events (AE's) from the various biopharm, bronchial challenge and single-dose tolerability studies. These data were reviewed and nothing really striking was seen in these studies which in many cases were not placebo-controlled, often single-dose and mostly in healthy volunteers.

The major source of the adverse event profile of Tilade is the pooled data from the 14 placebo-controlled trials in which 936 patients received the active drug and 933 received placebo. Adverse events were also reviewed for the two U.S. open-label, long-term safety trial.

10.2.1 ADRs FROM THE PLACEBO-CONTROLLED STUDIES

Table 10.2.1A below shows the frequency of ADRs reported by 1% or more in any one group in the 14 placebo-controlled studies. As seen in the individual pivotal trials, very few AE's could be directly attributed to Tilade. Taste perversion (or unpleasant taste) stands out as being more frequent on the active drug. Diarrhea is another event that appeared more frequently associated with the active drug than with placebo. A number of events appeared narrowly more frequent on Tilade than on placebo. These included chest pain, pharyngitis, gastroenteritis and mouth dryness.

Table 10.2.1A. Frequency (%) of Adverse Events (only events occurring at >1% in any one group, less frequent on placebo, and of relevance to the active drug pharmacology).

	Tilade (n=936)	Placebo (n=933)
URI	27	28
Bronchospasm	15	20
Coughing	15	17
Headache	13	14
Pharyngitis	13	10
Taste Perversion	4	1
Bronchitis	4	3
Influenza-like symptoms	4	3
Diarrhea	3	2
Chest pain	3	2
Dyspnea	1	3
Mouth dryness	1	0

Because of the broadness of the age for which this product will be indicated for, the safety data was analyzed by age group to see if peculiar adverse events occurred in any of the age groups. As shown in table 10.1.2B below, there were only few differences between the age groups in the AE profile. Pharyngitis was reported more frequently by the younger patients (especially 6-11 year old children) compared to the adults. Fever was also more commonly reported in the younger children compared to adults, and chest pain had a significantly higher frequency in the 6-11 year old patients. Headache which appeared more frequently on Tilade in some of the US pivotal trials seemed more common on placebo in the pooled controlled-trial data shown in table 10.2.1B. The rather large frequency of headache in the ≥66 year old placebo arm most likely reflects the small size of the group. Abdominal pain appeared more frequently reported by the 6-11 year old patients compared to the rest of the study population. Finally, although taste perversion occurred more on Tilade than placebo in all groups, the patients in the 12-65 year old group showed the greatest separation. Other than recognizing the trends in these various AE's, it is uncertain what real conclusions regarding the age group differences could be drawn.

TABLE 10.2.1B. **Adverse events by age groups (only events occurring at >1% in any one group, less frequent on placebo, and of relevance to the active drug pharmacology). Frequency expressed as percentages.**

	≤5 year		6-11 year		12-65 year		≥66 year old	
	Tilade n=264	Placebo n=255	Tilade n=259	Placebo n=261	Tilade n=396	Placebo n=399	Tilade n=17	Placebo n=17
Respiratory Disorders								
Bronchospasm	15	18	27	28	9	15	18	29
Coughing	19	22	24	23	6	10	12	6
Pharyngitis	11	92	21	15	8	8	0	0
Dyspnea	1	2	2	1	1	4	6	12
Chest pain	1	1	4	1	3	3	6	0
Body as a whole								
Fever	24	20	13	12	2	3	0	0
Headache	5	9	19	23	15	12	0	17
Convulsions	0	0	0	0	0	0	6	0
Gastro-intestinal system								
Diarrhea	5	2	3	1	2	2	6	0
Abdominal pain	2	2	5	2	1	2	0	6
Gastroenteritis	3	1	3	3	1	1	0	0
Special senses								
Taste Perversion	3	1	6	2	4	1	12	6
Conjunctivitis	4	5	4	2	1	1	0	0

An analysis was also carried out looking at the adverse event profile between the three different dosing regimens employed in the study: BID (n=77), TID (n=996) and QID (n=786). There were no dose-related trends in the main adverse events of interest except for taste perversion which occurred at 0, 4 and 6% frequency on the BID, TID and QID Tilade groups respectively, while it occurred at 2, 1 and 2% in the corresponding placebo groups. The only death reported in the controlled trials (details discussed below) occurred in the BID study.

Gender: Adverse events reported in the controlled studies were also reviewed by gender. Although overall there were more males than females in the pooled data, there was an acceptable gender balance between the active and placebo groups: 562 males on Tilade and 572 males on placebo; and 374 females on Tilade and 361 females on placebo. There were no major gender differences in the adverse event profile. Among the females in the study, diarrhea was more frequently reported on Tilade than on placebo (3% vs 1%) while gastroenteritis was more frequent on Tilade than on placebo in the males (3% vs 1%). Males also showed a greater separation between Tilade and placebo on taste perversion (5% vs 1%) compared to females 4% vs 2%. No other AE of significance showed a gender bias.

10.2.2 ADVERSE EVENTS BY BODY SYSTEM AND BY SEVERITY

As seen in section 10.2.1, a review of individual adverse events did not clearly separate Tilade and placebo on most events because the incidence was either low on both or high on both. The sponsor provided a tabulation of AE's based on body systems. A review of this tabulation also failed to show a significant distinction between Tilade and placebo on most body systems. Fifty-four percent (54%) of Tilade patients reported AE's in the respiratory system compared to 58% on placebo. The figures were 23% versus 20% respectively for the 'body as a whole' system; and 17% versus 18% for the CNS and peripheral nervous system. Only the 'special senses' showed a clear separation between Tilade and placebo: 4.7% versus 1.6%, and this was mostly due to the unpleasant taste reports.

The adverse events were also reviewed by severity. The classification of mild, moderate, severe or very severe was assigned by the investigator. Again, the frequency in each category was similar between Tilade and placebo. Only 'taste perversion' showed a clear difference. About 3.6% of patients reported mild to moderate taste perversion on Tilade compared to 1.6% in the same category on placebo. Nearly 1% of Tilade patients had taste perversion classified as severe to very severe while no placebo patients had any report in this category for taste perversion.

10.3 DEATHS, DROPOUTS AND OTHER SERIOUS AE's

10.3.1 DEATHS

As stated earlier, only one death occurred in the entire database of 16 controlled and uncontrolled trials in which 1,076 patients received Tilade for varying periods. The patient died in a non-US controlled study (CR 1366). She was a 48 year old patient with severe asthma, COPD and hypertension. Death was said to be due to myocardial infarction although no autopsy was done. The patient was also being treated with fenoterol MDI, beclomethasone MDI, theophylline tablets, and diuretics (unspecified).

10.3.2 DROPOUTS

Of the 936 patients who received Tilade in the 14 controlled (US and non-US) trials, 112 or 12% discontinued from the study. A comparable proportion, 124/933 or 13.3% discontinued from the placebo arms of the studies. Table 10.3.2 below summarizes the main reasons for withdrawal.

Table 10.3.2 MAIN REASONS FOR DROPOUTS (Controlled Trials)

	Tilade (n=936)	Placebo (n=933)
Dropout due to adverse events	56 (6%)	63 (6.8%)
Dropout due to lack of effect	3 (0.3%)	2 (0.2%)
Dropout for non-treatment related reasons	53 (5.7%)	59 (6.3%)
TOTAL	112	124

In the two open-label trial, 93 (or 33.6%) patients who received Tilade withdrew from the study. Fourteen (5%) did so due to adverse events, 6 (2.2%) due to lack of effect and 73 (26%) for non-treatment related reasons.

The reason for withdrawal in the individual patient was reviewed based on the detailed listing and patient by patient description provided by the sponsor. Attention was focussed on the category of patients who withdrew due to adverse events in the controlled trials shown in table 10.3.2 above (n=56 on Tilade and 63 on placebo). The most frequent AE leading to withdrawal was bronchospasm, and contributed wholly or partially to discontinuation in 26 out of the 56 dropouts on Tilade and 39 out of 63 on placebo. URI contributed to withdrawal in 7 Tilade and 11 placebo patients. Coughing was cited in 9 Tilade and 4 placebo patients, and dyspnea contributed to withdrawal in 4 Tilade and 5 placebo patients. Two events that appeared predominantly more on Tilade than on placebo were headache and dizziness. Seven patients dropped out wholly or partly due to headache compared to 2 on placebo. Similarly, 6 Tilade compared to 1 placebo patients withdrew due to dizziness. Many of the other AE's occurred in few patients in both study arms making causality difficult to assign to the events.

A review of dropouts due to AE's in the two open-label 52-week trials did not provide additional safety information on Tilade. As stated above, 14 patients withdrew from the study due to adverse events: 6 in the pediatric long-term trial (CR 2233A), and 8 in the adult long-term trial (CR 3004). Reasons for withdrawal in these cases were, in general, similar to those seen in the controlled 12-24 week trials. except for some psychiatric disorders seen in children. In the children study, reasons for withdrawal included rhinitis, coughing/vomiting/rash, hyperactive behavior and asthma exacerbation. In the adult trial, patients withdrew for such AE's as unpleasant taste, depression, URI, joint pains, lack of efficacy and asthma exacerbation. These findings confirm the safety of long-term use of Tilade.

10.3.3 OTHER SERIOUS ADVERSE EVENTS

The sponsor broadened the definition of 'serious' adverse events to include those events considered to be of major clinical significance even though they did not meet the regulatory definition of 'serious'. The AE's reported in this section were termed 'major' adverse events. Fifty-three (53) patients reported 56 major adverse events in the 16 clinical trials. Of the 53 patients, 39 were from the placebo-controlled, 12-24 week trials, while 14 were from the two 52-week trials. Twenty-three (23) of the 53 patients (43%) including one death, discontinued the trial due to the major AE.

The majority of the serious AE's were related to worsening asthma. About 48% of the events were thought

to reflect asthma exacerbation. Reported events included bronchospasm (10 on Tilade, 19 on placebo), coughing (2 on Tilade, 7 on placebo), dyspnea (1 Tilade, 5 placebo), and URI (2 each on both arms). Other events included rhinitis, sinusitis, fever, dizziness and abdominal pain. Most of these did not differ in frequency between Tilade and placebo. There was a large discrepancy in the occurrence of psychiatric disorders between Tilade and placebo. The reported events in this category included personality disorder, impaired concentration, agitation, emotional lability, nervousness, aggressive reaction, depression, somnolence and suicide attempt. The 17 reports of psychiatric disorders with the exception of the suicide attempt occurred in patients receiving placebo. Virtually all the patients involved were children. The sponsor speculated that some of the reactions might be related to the D&C Yellow No. 10 additive used in blinding of the trials, and also a reflection of the behavioral response to a chronic illness or poor asthma control.

10.4 LABORATORY EVALUATION

Laboratory monitoring of hematology and biochemistry variables was performed in the 16 therapeutic trials, as previously discussed in the review of individual studies. Most patients enrolled in the study had normal baseline laboratory measurements. There were some 'shifts' from normal in most studies. These shifts mainly reflected predefined statistical deviations from the mean. They occurred at comparable rates between Tilade and placebo. For example, the occurrence of abnormal hematology value shifts was 7.1% on Tilade and 7.8% on placebo, in the 14 pooled placebo-controlled trials. These shifts included WBC counts, eosinophil count and platelet count, and were not grossly different in size or direction between placebo and Tilade.
Similarly, on-study changes in biochemistry and urinalysis variables occurred at comparable frequency between Tilade and placebo. Overall therefore, no distinct lab findings could be attributed to Tilade per se from these trials.

10.5 POST-MARKETING EXPERIENCE

The sponsor stated that Tilade Nebulizer Solution was only available in Italy at the time of the filing of the NDA. They claimed there were no adverse event reports from Italy on the drug, although it is unclear to this reviewer how the reporting system in Italy operates. The sponsor also referred to the Tilade MDI which has been approved in the UK since 1986, in the US since 1992 and in many other countries. Although no summary of the post-marketing safety reports on the MDI was provided in the current NDA, the sponsor made a statement that "nothing from the post-marketing experience reported to date...suggest any specific concern about the use of Tilade Inhaler' or the nebulizer solution.

10.6 CONCLUSIONS ON SAFETY OF TILADE NEBULIZER SOLUTION

The data reviewed above support the safety of Tilade Nebulizer Solution given at doses of 11 mg two, three or four times per day over periods as long as 52 weeks. Adverse events that could be directly attributed to the drug were minimal. Taste perversion appeared to be the only one which may be causally related. While this raises concerns about the possibility of unblinding during the trials, and of compliance problems during use in the real world, unpleasant taste is a well-known adverse event of the Tilade drug substance. Other AE's such as URI, asthma exacerbation, bronchospasm etc. may reflect underlying disease, especially since the incidence did not differ substantially between active drug and placebo. Only one death occurred in the studies, possibly reflecting the mildness of the population studied, and the larger

proportion of children in the database.
Subgroup assessment of the population studied did not show any predisposition to adverse events by age or gender. The sponsor did not carry out an analysis of the adverse event profile based on race. While there is no pharmacologic reason to suspect an abnormality in this regard, it does represent an important omission.

Overall, the safety profile defined by this database did not show any surprises unanticipated by the larger database in existence on the Tilade MDI.

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