SEP 17 1999

Statistical Review

NDA21-009
Name of Drug: Nedocromil Sodium 2% Ophthalmic Solution (NSO 2%), BID
Applicant: Allergan, Inc.
Indication: For the prevention and treatment of allergic conjunctivitis
Documents Reviewed: Statistical and Clinical sections of NDA
Reviewer: Qian Li, Sc.D.
Date of Review: May 1999-September 1999

Introduction:

It is hypothesized that NSO 2% exerts its effects through preventing the release of multiple mediators of inflammation in treating allergic conjunctivitis (AC). In a labeling statement proposed by the sponsor, this NDA pursues the approval of the treatment and prevention of allergic conjunctivitis using a twice daily dosing frequency.

In this statistical review, the focus is on efficacy evaluation of NSO 2% on the treatment of AC. The first section of the review discusses study selection. Since more than two pivotal studies have been conducted to evaluate the treatment effect of NSO 2% with AC patients, it is important to avoid any biased selection of studies in efficacy evaluation. The second section discusses the endpoints and statistical issues. The third section presents the review of ten efficacy studies and analysis. Discussion on conclusion is presented in the last section. An appendix is attached to this review for some analyses on data sets that was entered by the review medical officer.

I. Study selection:

Thirty-one studies of NSO 2% were conducted on various indications. Of those, twenty-one were for the indication of AC. Of the 21 AC studies, sixteen were seasonal allergic conjunctivitis (SAC) studies and 5 were perennial allergic conjunctivitis (PAC) studies. Of the 16 SAC studies, ten were conducted using BID regimen for the purpose of evaluating efficacy and safety of NSO 2%.

All of the ten studies were placebo controlled, randomized and double blinded clinical trials conducted during peak pollen period with adequate sample sizes. The 10 studies were CR 1170/1, CR 1170/2, CR 1342, CR 1344, CR 1959, CR 1871, CR 1156, CR 1891, CR 1242, and CR 1901. Seven of these 10 studies were conducted in North America during the ragweed pollen season and 3 were conducted in Europe during birch pollen season. One of these European studies, CR 1871, was conducted in a young population age 6 to 16 years. The rest of the study has patient population aged 7 years and older.

Of these 10 studies, the sponsor has identified only 5 studies to provide primary evidence in pursuing treatment effect in itching and redness of allergic conjunctivitis. The 5 studies are CR 1170/1 & CR 1170/2, CR 1342 & CR 1344, and CR 1959. The 5 studies that were

not included in sponsor's efficacy evaluation were CR 1871, CR 1156, CR 1891, CR 1242, and CR 1901. The reasons of excluding these studies are discussed in the individual study review in later section. The information of the 5 studies selected by the sponsor was better organized, while the information for the rest of studies was not only very poorly organized but also incomplete. After a preliminary review of all the ten studies, both the medical officer and this reviewer agree that it is appropriate to include all the 10 studies for efficacy evaluation. The similarity of the ten studies made them equally important for efficacy assessment of NSO 2% on BID regimen in treating patients with AC.

II. Statistical issues:

Efficacy Variables (Endpoints):

In a meeting between the sponsor and the agency in 1991, it was required by the agency that itching and redness should be the primary endpoints to support efficacy claims of treatment in allergic conjunctivitis. The treatment effect can be either itching or redness, or both, and the label will reflect the treatment effect on allergic conjunctivitis.

In all of the 10 studies, itching was assessed in patient's diary. The redness was assessed by clinician in some studies and by patients in patient's diary in others. For assessments made both by clinicians and patients, five scale score was used for both itching and redness, 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe. It should be mentioned here that neither itching nor redness was pre-specified as primary endpoint in all of the ten studies.

For the end points recorded in patient's diary, the average across the peak pollen period was used in analysis. When baseline score was adjusted, the daily baseline scores were averaged across the baseline period. For those studies that did not define baseline period clearly, the last 7 days before the start of treatment were used as baseline period. For the score assessed by clinicians, the scores from one peak pollen visit (Visit 4) and a baseline visit were used.

Methods of statistical analysis:

Five of the 10 allergic conjunctivitis studies were analyzed using Koch's approach, the other 5 studies were analyzed using Wilcoxon rank sum tests including Kruskal Wallis and Mann-Whitney tests. Koch's approach is a stratified non-parametric analysis with the flexibility of adjusting covariate, while Mann-Whitney U test is a simple non-parametric analysis without considering stratification factor and covariate. Although there are advantages in Koch's approach over Wilcoxon tests, when sample size became smaller in each stratum, it is difficult to assess if those advantages still exist. In this NDA, center was the stratification factor and the sample size was not large in each stratum in all of the studies. Therefore both approaches should be appropriate.

Since no consistent analysis was specified in the ten studies and the computational tool for Koch's approach is not available, Mann-Whitney U-tests adjusting baseline difference (i.e., change from baseline) are used in this review and one-sided p-values are calculated. However, such analyses have not been carried out completely due to unavailability of SAS data sets of some studies.

The intend-to-treat (ITT) analysis should be used for efficacy evaluation. However, this has not been accomplished due to missing information in some studies and unavailable data sets.

As suggested by medical officers, one-sided p-values generated by Mann-Whitney U tests without adjusting baseline are also calculated and listed in this review. However, this type of analysis is not appropriate when there is baseline difference. It is not appropriate to set statistical significant level at 0.05 for baseline difference. On the other hand, the change from baseline analysis is similar to the straight comparison during peak pollen period when there is no baseline difference. The variability of change from baseline is not increased by introducing baseline as it is concerned by the medical officers. This can be seen from the data provided for this NDA. The explanation is that the variability of baseline is similar to that of the measurement in peak pollen period and there is positive correlation between baseline scores and scores in peak pollen period.

Multiplicity issues:

At least two major sources of multiplicity existed in this NDA. One was from multiple endpoints, itching and redness. The other arose from multiple studies.

In this NDA, the sponsor has presented a pooled analysis to address the issue of multiple studies. The pooled analysis pooled information from five studies selected by the sponsor. Such a pooled analysis is not acceptable, since the five studies only represented part of the whole information. The sponsor has failed to discuss the issue of multiple end points.

III. Review of individual studies:

In the following review, the 5 studies selected by the sponsor for efficacy evaluation are reviewed first, followed by the other 5 studies. The sponsor only provided SAS data sets for the five studies selected for efficacy evaluation. SAS data sets are not available for the other 5 studies. Request for the data sets were sent on 7/16/99. Since this NDA was bought from another company and the data was processed by an European company, the sponsor was unable to provide the data sets within the frame of review timeline.

The format of the individual study review basically includes three tables for each study, one for patient accounting information, one for pollen counts, and the other for the results of statistical analysis. Part of the information in those tables is based on the re-analysis and calculation by the reviewer. Some cells in these tables are empty simply because no accurate information was provided by the sponsor.

The peak pollen period was chosen based on the pollen measurement at study centers. Such measurement did not reflect individual patient's pollen exposure. Therefore the pollen counts presented in the tables were not reliable information for individual patient's actual exposure.

III.A Studies selected by sponsors for efficacy evaluation:

CR 1170/1 & CR 1170/2 were multi-center, double blinded, placebo-controlled, group-comparative studies conducted according to the same protocol during the ragweed pollen season in 1986 in America. There were 3 centers in CR 1170/1 and 4 in 1170/2. Patient accounting information was summarized in Table 1170/1–1 and Table 1170/2–1.

Table 1170/1-1

Number of patients	NSO 2%	Placebo
Randomized	47	47
Receiving treatment	43	43
Complete study	42	38
Withdrawal	1	5
Treatment failure	0	0
Dropout due to AE	1	1
Other dropouts	0	4

Table 1170/2-1

Number of patients	NSO 2%	Placebo
Randomized	60	57
Receiving treatment	52	53
Complete study	47	51
Withdrawal	5	2
Treatment failure	0	0
Dropout due to AE	4	0
Other dropouts	1	2

The first three weeks of the treatment, from 8/22-9/11 inclusive was designated as the peak pollen period for all clinics for Study CR 1170/1. The pollen count of peak pollen period against background was summarized in Table 1170/1–2. For Study CR 1170/2, the first 14 days of treatment from 8/23-9/5 inclusive was designated as the peak pollen period for all clinics. The pollen count information in peak pollen period and background was summarized in Table 1170/2–2. Note the background pollen count information was obtained during the study period subtracting the peak pollen period.

Table 1170/1-2

Location/ Center	Peak period	Peak period (grain/m^3)			Background (grain/m^3)		
		Mean	Min	Max	Mean	Min	Max
Chelmsford,MA	8/22 – 9/11	180			18		
Rochester, NY	8/22 - 9/11	630			31		

Milwaukee, WI	8/22 – 9/11	825	44	2587	55	80	296

Table 1170/2-2

Location/ Center	Peak period	Peak period (grain/m^3)			Background (grain/m^3)		
		Mean	Min	Max	Mean	Min	Max
Englewood,CO	8/23 – 9/5	79			22		
Chicago, IL	8/23 – 9/5	355			88		
Des Plaines, IL	8/23 – 9/5	1189			222		
Minneapolis, MN	8/23 – 9/5	1280			238		

The study results on itching and redness were summarized in Table 1170/1–3 and Table 1170/2–3 for CR 1170/1 and CR 1170/2 respectively. For itching, the analysis adjusted by baseline showed statistically significant treatment difference in favor NSO 2% in Study CR 1170/1, while the difference was not significant in Study CR 1170/2. For redness which was assessed by clinician at clinical visits, Study CR 1170/1 showed statistically significant improvement in NSO 2% treatment group compared to placebo, while Study CR 1170/2 failed to show treatment difference.

Table 1170/1-3

Treatment	Mean score for itching			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.18 (40)	1.51 (40)	0.33 (40)			
NSO 2%	1.14 (42)	1.09 (42)	-0.05 (42)	0.001	0.003	0.002

Treatment	Mean score for redness by clinician			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.05 (42)	1.29 (42)	0.23 (42)			
NSO 2%	1.14 (43)	1.00 (43)	-0.14 (43)	0.038	0.016	0.038

Table 1170/2-3

Treatment	Mean score for itching			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.51 (53)	1.48 (53)	-0.03 (53)			
NSO 2%	1.44 (50)	1.19 (50)	-0.25 (50)	0.33	0.176	0.028

Treatment	Mean score for redness by clinician			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.36 (53)	1.27 (52)	-0.10 (52)			
NSO 2%	1.27 (51)	1.22 (50)	-0.06 (50)	0.745	0.472	0.327

CR 1343 and CR 1344 were also multi-center, double blinded, placebo-controlled, group-comparative studies conducted according to the same protocol during the ragweed pollen season in 1987. There were 4 centers for CR 1343 and 5 centers (4 locations) for CR 1344. Patient accounting information was summarized in Table 1343–1 and Table 1344–1 for CR 1343 and CR 1344 respectively.

Table 1343-1

Number of patients	NSO 2%	Placebo
Randomized	58	63
Receiving treatment	58	63
Complete study	57	63
Withdrawal	1	0
Treatment failure	0	0
Dropout due to AE	1	0
Other dropouts	0	0

Table 1344-1

Number of patients	NSO 2%	Placebo
Randomized	69	71
Receiving treatment	69	71
Complete study	63	69
Withdrawal	6	2
Treatment failure	0	1
Dropout due to AE	0	0
Other dropouts	6	1

The studies were conducted from July 15, 1987 through Oct. 17, 1987. The baseline period was planned to coincide with the start of the ragweed pollen season. The information in peak pollen period was summarized in Table 1343-2 and Table 1344-2 for Studies CR 1343 and CR 1344 respectively.

Table 1343-2

Location/ Center	Peak period	Peak period (grain/m^3)			Background (grain/m^3)		
		Mean	Min	Max	Mean	Min	Max
Cincinnati,OH	8/22 – 9/11	116.4			18.6		
Norristown, PA	8/21 – 9/10	215.9			22.5		
Detroit, MI	8/21 – 9/10	102.5			21.2		
Rochester, NY	8/20 – 9/9	85			7.6		

Table 1344-2

Location/ Center	Peak period	Peak period (grain/m^3)			Background (grain/m^3)		
		Mean	Min	Max	Mean	Min	Max
Chicago, IL	8/21 – 9/10	131.1			26.7		
Minneapolis,MN	8/21 – 9/10	148.8			23.9		
Iowa city, IA	8/21 – 9/10	200.1			91.2		
Prairie Village,KS	8/21 – 9/10	353.5			47.6		

The study results on itching and redness were summarized in Table 1343–3 and Table 1344–3 for CR 1343 and 1344 respectively. For itching, both studies showed significant treatment differences in favor of NSO 2% (CR 1344 was statistical significant, CR 1343 was close to statistical significant). For redness which was assessed by clinician at clinical visits, only Study CR 1344 showed statistical significance in favor of NSO 2%.

Table 1343-3

Treatment	Mean score for itching			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.10 (63)	1.27 (63)	0.17 (63)			
NSO 2%	1.30 (58)	1.18 (58)	-0.12 (58)	0.12	0.027	0.175

Treatment	Mean score for redness by clinician			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.0 (63)	1.0 (63)	0 (63)			
NSO 2%	1.05 (58)	1.0 (58)	-0.05 (58)	0.93	0.304	0.556

Table 1344-3

Treatment	Mean score for itching			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.31 (71)	1.49 (71)	0.18 (71)			
NSO 2%	1.51 (67)	1.37 (67)	-0.13 (67)	0.09	0.010	0.175

Treatment	Mean score for redness by clinician			Koch's p-value (2-sided)	Mann-Whitney p-value	
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline
Placebo	1.08 (71)	1.21 (71)	0.127 (71)			
NSO 2%	1.09 (69)	0.83 (71)	-0.26 (69)	0.005	0.004	0.002

CR 1959 was a double blinded, three arm study comparing NSO 2%, Opticrom 4%, and placebo. This study was conducted in 1989 in ragweed season. Patients randomly received either NSO 2% or Opticrom 4% (active control) or placebo. Study drug was administered as one drop per eye four times daily. The NSO 2% group received NSO 2% twice daily plus placebo twice daily. The placebo group received placebo four times daily and Opticrom group received Opticrom four times daily. Note, this study was slightly deviated from BID regimen. Nevertheless, this study provide valid comparison between NSO 2% BID regimen and placebo treatment groups. Patient accounting information was summarized in Table 1959-1.

Table 1959-1

Number of patients	NSO 2%	Opticrom	Placebo
Randomized	116	115	58
Receiving treatment	116	115	58
Complete study	110	112	57
Withdrawal	6	3	1
Treatment failure	0	0	0
Dropout due to AE	1	0	1
Other dropouts	5	3	0

Patients were screened between July 12 to August 9, 1989. The study consisted of a one-week baseline which began approximately during the first week of the 1989 ragweed season for the area in which the study was conducted (August 16 – August 23), followed

by a six week drug treatment period (August 23 – October 4). Pollen count information was summarized in Table 1959–2.

Table 1959-2

Locations/Centers	Peak period	Peak pollen period (grains/m^3)			Background (grains/m^3)		
		Mean	Min	Max	Mean	Min	Max
Minneapolis, MN	8/23 – 9/5	126.9			18.7		
Milwaukee, WI (Fink)	8/25 – 9/7	135.4			19.9		
Milwaukee, WI (Hirsch)	8/23 – 9/5	172.9			16		
Gross Pointe Woods, MI	8/23 – 9/5	126.7			9.8		
Cincinnati, OH	8/23 – 9/5	234.3			10.7		
Chelmsford, MA	8/23 – 9/5	67.3			1.5		
Norfolk, VA	8/23 – 9/5	22			8.3		
Lenexa, KS	8/24 – 9/6	598.6			98.8		
Novi, MI	8/23 – 9/5	114			14.4		
Chicago, IL	8/23 – 9/5	160.9			16.9		

The results on itching and redness were summarized in Table 1959–3. The redness was assessed by clinician at a clinical visit. Neither the comparison between NSO 2% and placebo or between the Opticrom and placebo has shown statistical significant difference on itching and redness.

Table 1959-3

Treatment	Mean score for itching			Koch's p-value (2-sided)	Mann-Whitney p-value		Kruskal-Wallis (Adj. Base) (2-sided)
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline	
Placebo	1.47 (57)	1.59 (57)	0.11 (57)				
NSO 2%	1.35 (112)	1.27 (112)	-0.08 (112)	0.072	0.071	0.014	
Opticrom	1.40 (115)	1.41 (115)	0.01 (115)	0.262	0.258	0.117	0.34

Treatment	Mean score for redness			Koch's p-value (2-sided)	Mann-Whitney p-value		Kruskal-Wallis (Adj. Base) (2-sided)
	Baseline	Peak period	Difference		Adjust baseline	Not adjust baseline	
Placebo	0.46 (51)	0.82 (57)	0.36 (57)				
NSO 2%	0.41 (112)	0.70 (112)	0.29 (112)	0.22	0.387	0.194	
Opticrom	0.36 (115)	0.70 (115)	0.34 (115)	0.796	0.574	0.225	0.85

III.B Studies not included for efficacy evaluation:

CR 1871 was a multi-center, double-blind, placebo-controlled, group-comparative study conducted in Sweden during birch pollen season in 1989 in children age 6 to 16 years. Patients entered the study on a predetermined date just before the birch pollen season began, following a pre-trial visit prior to the start of the treatment period. Patients were randomly allocated to receive either active treatment or placebo for a period of 4 weeks in BID. Four centers (Vasteras, Norrkoping, Linkoping, and Umea) participated in this study. Patient accounting information was summarized in Table 1871–1.

Table 1871-1

Number of patients	NSO 2%	Placebo

Receiving treatment	77	72
Complete study	77	70
Withdrawal	0	2
Treatment failure	0	0
Dropout due to AE	0	0
Others	0	2

Study duration was between April 1989 to June 1989. The pollen count information was recorded daily between April to June. Only mean peak pollen count information was available (see in Table 1871– 2). The only information for background pollen count was that daily pollen count was above 100 grains/m3 for all the period that pollen count was recorded. Although it is difficult to compare the difference of pollen challenge between peak season and background, it is clear that the pollen challenge was reasonable.

Table 1871-2

Location/ Center	Peak period	Peak pollen period (grain/m^3)			Background (grain/m^3)		
		Mean	Min	Max	Mean	Min	Max
Vasteras	4/24 – 5/10	751.6					
Norrkoping/ Linkoping	4/24 – 5/10	505.9					
Umea	5/15 – 5/28	995.4					

* Cells are empty due to incomplete information provided by sponsor.

The analysis in peak pollen season without adjusting baseline scores showed statistical significant difference for itching and approaching statistical significance for redness in favor to NSO 2%. The p-values are listed in Table 1871–3. However, the daily itching scores of baseline showed that a large difference existed between the two treatments. The mean scores calculated by hand were also listed in Table 1871–3. Since no SAS data set was provided by the sponsor, it was very difficulty to further evaluate the baseline difference in both itching and redness scores and its impact on statistical analysis. Therefore it is difficult to judge the validity of the statistical results provided by the sponsor.

Table 1871-3

Treatment	Mean score for itching			Mann-Whitney p-value	
	Baseline	Peak period	Difference	Adjust baseline	Not adjust baseline
Placebo	0.81 (62)	1.4 (72)			
NSO 2%	0.61 (72)	0.9 (75)			0.002

* Cells are empty due to incomplete information provided by sponsor.

Treatment	Mean score for redness			Mann-Whitney p-value	
	Baseline	Peak period	Difference	Adjust baseline	Not adjust baseline
Placebo		0.9 (72)			
NSO 2%		0.6 (76)			0.027

* Cells are empty due to incomplete information provided by sponsor.

CR 1156 was a multi-center, placebo-controlled, group-comparative study conducted in the Canadian ragweed pollen season (August to October) of 1986. The study was conducted in five weeks, including one week baseline period followed by 4 weeks of treatment. Three centers in Ontario, Canada participated in this study. Patient accounting information was summarized in Table 1156–1.

Table 1156-1

Number of patients	NSO 2%	Placebo
Enter study	60	61
Receiving treatment	49	54
Complete study	49	51
Withdrawal	0	3
Treatment failure	0	0
Dropout due to AE	0	0
Others	0	3

The period of peak pollen challenge occurred between 8/20 - 8/26 (107 grains/m^3) and 8/31 – 9/10 (79.1 grains/m^3). For the purpose of analysis, the result in the period of 8/20 – 8/26 was reviewed because the mean pollen count was above 100 grains/m^3 in that period. The reviewer has requested daily pollen count information during the study period and a clearer copy of figure on pollen count, unfortunately, the sponsor was unable to provide it.

Based on the statement in study report, patient's diary data showed no statistically significant difference between the two treatment groups during peak pollen season for itching and redness. Mann-Whitney U-test scores were reported only (899 for itching and 852 for redness). The reviewer did not feel comfortable to convert the scores to p-values without data sets. The SAS data set was not available as it was mentioned before. Also notice that the analysis provided by the sponsor was not intent-to-treat analysis. Many patients were excluded from efficacy analysis for protocol violation. ITT analysis should be explored if the SAS data set was available.

Table 1156-3

Treatment	Mean score for itching			Mann-Whitney Test score (Adjust baseline)
	Baseline	Peak period	Difference	
Placebo	1.12 (50)	1.43(46)	0.29 (44)	
NSO 2%	1.05 (48)	1.17 (42)	0.23 (41)	899

Treatment	Mean score for redness			Mann-Whitney Test score (Adjust baseline)
	Baseline	Peak period	Difference	
Placebo	0.78 (50)	1.12 (46)	0.28 (44)	
NSO 2%	0.75 (48)	0.83 (42)	0.15 (41)	852

The reviewer does not find the reasons for excluding this study from efficacy evaluation is convincing. The reasons were that the sample size was inadequate, the study suffered from low pollen challenge and there was excessive escape medication use. Comparing to Study CR 1170/1 which had even smaller sample size than this study, the sample size should not be the reason to exclude the study since Study CR 1170/1 was included in efficacy analysis. The pollen count at peak period indeed seemed to be low. However, without background information, it is difficult to judge if there was sufficient challenge. Nevertheless, the number of pollen count met the sponsor's own criteria of study selection to include in the study. No discussion on the use of excessive escape medicine in study report except a comment on a relative balanced anti-histamine usage.

As it can be seen from Table 1156-1 for patient accounting information, 18 patients entered the studies but did not receive (or were not confirmed to receive) treatment. For those patients who were not confirmed if treatment was started, conservative approach should be applied to impute the missing information for ITT analysis.

CR 1891 was a multi-center, placebo- and active-controlled, group-comparative study conducted in the Canadian ragweed pollen season of 1989. Patients in NSO 2% treatment group receiving NSO 2% eye drops and placebo tablets, patients in terfenadine group receiving terfenadine and placebo eye drops and patients in placebo receiving both placebo eye drops and tablets. Again, this study was not a pure BID regimen by design. However, this study still provided valid base for BID regimen comparison.

Table 1891-1

Number of patients	NSO 2%	Terfenadine	Placebo
Receiving treatment	89	89	90
Complete study	84	85	87
Withdrawal	5	4	3
Treatment failure	4	2	2
Dropout due to AE	1	1	1
Other dropouts	0	1	0

Patients entered the study between 7/24 – 8/16, 1989. The peak pollen period was taken as 8/23 – 9/9, 1989. The average peak pollen counts were reasonably high in all the centers (about 300 counts/m^3) except one center (54.5 counts/m^3). Table 1891-2 covered pollen count information.

Table 1891-2

Location/ Center	Peak period	Peak pollen period (grain/m^3)		
		Mean	min	max
Drs. Alexander & Rosen	8/23 – 9/9	307.7		
Dr. Dolovich	8/23 – 9/9	54.5		
Drs. Yang & Drouin	8/23 – 9/9	295.8		

* Cells are empty due to incomplete information provided by sponsor.

Kruskall-Wallis statistic was used to compare three treatment groups. No statistical significant differences were observed in efficacy analyses among the three treatment groups (not adjust baseline). The Mann-Whitney pairwise comparisons were not reported and can not be generated because SAS data sets are not available for the same reason mentioned before. Baseline difference and intent-to-treat analysis should be explored once the data set is available.

Treatment	Mean score for itching			Mann-Whitney p-value (vs. placebo)	Kruskall-Wallis p-value (2-sided)
	Baseline	Peak period	Difference		
Placebo		1.24 (81)			
NSO 2%		1.18 (79)			
S. Cromoglycate		1.19 (83)			0.976

* Cells are empty due to incomplete information provided by sponsor.

Treatment	Mean score for redness			Mann-Whitney p-value (vs. placebo)	Kruskall-Wallis p-value (2-sided)
	Baseline	Peak period	Difference		
Placebo		1.10 (81)			
NSO 2%		0.96 (79)			
S. Cromoglycate		0.95 (83)			0.575

* Cells are empty due to incomplete information provided by sponsor.

The reviewer does not think the reason to remove the study from efficacy evaluation is legitimate. The reason for not including this study was that the active control, Terfenadine, did not show efficacy over placebo. In general, in a trial with both placebo and active controls, the comparison between placebo and the tested drug is of primary interest. Active control should not be used as the validity check of the primary comparison. As it was the case in Study CR 1959 which also had both placebo and active controls, the active control did not show statistical significant difference over placebo in that study. However, Study CR 1959 was included in efficacy evaluation. There was an obvious inconsistency in study selection.

CR 1242 was a multi-center, placebo-controlled, group-comparative study conducted in Finland during the birch pollen season of 1987. The study included a phase of recruitment, followed by two weeks of pre-pollen period, and 4 weeks of pollen challenge period. Patients aged 7 years and older were recruited into the study. The patient accounting information was summarized in Table 1242-1. In this table, it was assumed that all the patients received treatment since no discussion on patient withdrawal before treatment started in the report.

Table 1242-1

Number of patients	NSO 2%	Placebo
Enter study (randomized)	64	63
Receiving treatment	64	63
Complete study	57	51
Withdrawal	7	12
Treatment failure	3	6
Dropout due to AE	2	0
Other dropouts	3	6

The study started on 4/28 and ended on 5/18, 1987. Birch pollen counts were recorded daily in three study centers (Kuopio, Helsinki and Oulu) between April 20 and June 22 in 1987. Pollen accounting information was summarized in table 1242–2.

Table 1242-2

Location	Peak period	Peak pollen period (grain/m^3)		
		Mean	min	max
Kuopio	5/15 – 5/24, 5/30 – 6/4	946		
Oulu	5/16 – 5/19, 5/29 – 6/7	1330		
Helsinki	5/14 – 5/28	4302		

Direct comparisons of the symptom scores on itching and redness from patient's diary recorded during the peak pollen period were used in the two treatment groups. No specific p-value was reported. It is unclear how the patient withdrawal information was incorporated in the analysis. This was an obvious concern as patient count in Table 1242-1 showed imbalance in patient withdrawal between the two treatment groups. Baseline assessment was needed as well. The data sets were not available for the same reason mentioned before.

Table 1242-3

Treatment	Mean score for itching			Mann-Whitney p-value (Not adjust baseline)
	Baseline	Peak period	Difference	
Placebo		1.36 (54)		
NSO 2%		1.11 (56)		0.05<p<0.10

* Cells are empty due to incomplete information provided by sponsor.

Treatment	Mean score for redness			Mann-Whitney p-value (Not adjust baseline)
	Baseline	Peak period	Difference	
Placebo		0.96 (54)		
NSO 2%		0.76 (56)		Not Significant

* Cells are empty due to incomplete information provided by sponsor.

The report has indicated that the antihistamine usage in placebo treatment group was statistically significantly higher than NSO 2% group. In efficacy review, if no treatment difference is observed, such finding has no impact on efficacy result.

The study was excluded from the efficacy evaluation because drug supply arrived two weeks later after study started. According to the sponsor, "the late arrival of the drug supplies rendered difficulty to interpret the study result as the worst affected patients dropped from the study before treatment started due to intolerable symptoms".

However, after reviewing patient withdrawal information in study report, I have found no patient withdrew from the study before treatment started, instead 19 patients withdrew after treatment started. The reasons of withdraw are summarized in patient accounting table for this study. This showed the randomization scheme was well kept to the start of treatment. Despite the late arrival of drug supply, the patients still received sufficient

pollen challenge as it can be seen from the pollen count table. Therefore, the late arrival of study medication did not constitute the reason to remove this study from efficacy evaluation.

CR 1901 was a multi-center, placebo-controlled, group-comparative study conducted in Finland during the birch pollen season. After a period of one to two weeks of baseline, patients were randomly allocated to receive one of the following treatment for a period of four weeks: NSO 2% eye drops BID + placebo eye drops BID; Sodium cromoglycate eye drops QID and placebo eye drops QID. Patient accounting information was summarized in Table 1901-1. Again, this study was not a pure BID regimen, it nevertheless provided valid base for BID regimen comparison.

Table 1901-1

Number of patients	NSO 2%	S. Cromoglycate	Placebo
Receiving treatment	60	61	64
Complete study	55	59	60
Withdrawal	5	3	4
Treatment failure	3	1	1
Dropout due to AE	3	1	0
Other dropouts	0	1	3

This study was commenced between March – June 1989. Birch pollen counts were recorded daily in Kuopio, Oulu and Hurku between 4/12 – 6/13, 1989. The pollen count information was inconsistent between clinical and statistical reports in this study. The following table summarized pollen count information for this study from statistical report.

Table 1901-2

Location	Peak period	Peak pollen period (grain/m3)		
		Mean	Min	Max
Joensui	5/4 – 5/18	1241		
Pori	5/4 – 5/13	242		
Tampera	4/26 – 5/10	951		
Oulu	5/12 – 5/26	2375		
Kajaani	5/12 – 5/26	2375		
kuopio	5/4 – 5/18	1241		
Turku	4/26 – 5/10	951		

For itching assessed by patients, comparison between NSO 2% and placebo did not show statistical significant difference. The Mann-Whitney p-value is 0.086 without adjusting baseline difference. The analysis did not use ITT population. No pairwise comparison was given for redness score assessed by patient's diary. No further analysis can be done because data was not available.

Table 1901-3

Treatment	Mean score for itching			Mann-Whitney p-value (no baseline) (vs. placebo)	Kruskall-Wallis p-value
	Baseline	Peak period	Difference		

Placebo		1.37 (56)			
NSO 2%		1.14 (52)		0.086	
S. Cromoglycate		1.05 (56)		0.016	0.044

* Cells are empty due to incomplete information provided by sponsor.

Treatment	Mean score for redness			Mann-Whitney p-value (vs. placebo)	Kruskall-Wallis p-value
	Baseline	Peak period	Difference		
Placebo		0.87 (56)			
NSO 2%		0.86 (52)			
S. Cromoglycate		0.76 (56)			0.750

* Cells are empty due to incomplete information provided by sponsor.

The study was excluded by sponsor from efficacy evaluation for the reason that the study did not enter the majority of patients until there was a very high pollen challenge. Statistically, this did not constitute a reason to remove a study from efficacy evaluation. The prolonged recruitment period indeed could increase the variability in baseline, however, this variability can be taken into account by a analysis properly adjusting baseline.

IV. Conclusion:

All 10 studies reviewed were similarly conducted except there were relatively higher patient withdrawal rates in Studies CR 1156 and CR 1242 compared to the other studies. None of the 10 studies has any major deficiency that constitutes a reason to be removed from efficacy evaluation.

As it can be seen from the review, of the 10 studies, only five studies have provided reasonably reliable information on the assessment of treatment efficacy. In these five studies, NSO 2% was shown statistically significantly superior to placebo at the one-sided significance level 0.025 in two studies for both itching and redness. The rest of p-values ranged from 0.027 to 0.176 for itching and 0.304 to 0.472 for redness. None of the results from the other five studies were reliable due to insufficient data and missing data problems.

An overall conclusion of treatment effect of NSO 2% on AC is difficult to draw due to incomplete information provided by the sponsor. A conclusion based on partial information can be biased. To make efficacy conclusion, complete information should be provided and appropriate analyses should be done. Once all data are available and appropriate analyses are performed, a proper statistical methodology should be used to make an overall statistical significant assessment by examining all 10 p-values together.

Appendix: Analyses on Data Entered by the Medical Officer

Since the sponsor has been unable to provide SAS electronic data sets for five studies, the medical officer has entered the data herself based on hard copy data. Hard copy data from four studies (CR 1891, CR 1871, CR 1156 and CR 1242) were available in this NDA. Because many problems presented in these data sets, the result of the analysis based on these data sets is summarized in this appendix instead of the main body of the review. Caution should be exercised in interpreting the analysis results and to draw conclusions.

Several problems occurred in these data sets. The biggest problem in these data sets was the baseline information. The definition of baseline as mentioned before was the last 7 day before patients received treatment. However, the baseline information in these data sets contained days that patients received treatment. As it can be seen from the following tables, three studies have shown relatively large baseline difference, with Nedocromil treatment groups having lower scores than the placebo treatment group. It is difficult to tell if the baseline differences were contaminated by treatment effect (it there is any).

Missing data is another issue in these data sets. For patients who had protocol violation and withdrawal, some had partial data missing, and some had no data at all. CRFs were requested from sponsor to further confirm the missing data. How to handle missing data is another issue here. The medical officer has requested last-observation-carry-forward approach for all missing data for ITT analysis. However, it was specified in some protocols that missing data due to lack of efficacy should be imputed with the worst score.

There were a few places that data were altered. Some patients had itching or redness score 5 while the data scale should have been be 0-4. It was unclear why 5 was entered. The medical officer replaced all 5 to 4.

For the definition of peak pollen periods for these four studies, please refer to medical officer's review.

The results of per protocol and modified ITT analyses are listed in the following tables. There is no data imputation for per protocol analysis. The ITT analysis is modified because of the missing data problem.

Study 1891 - Per Protocol

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	1.03 (80)	1.20 (78)	0.21 (78)		
NSO 2%	1.10 (79)	1.12 (77)	0.02 (77)	0.013	0.354
S. Cromoglycate	1.02 (80)	1.19 (80)	0.16 (80)	0.112	0.490

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.94 (80)	1.08 (78)	0.15 (78)		
NSO 2%	0.85 (79)	0.91 (77)	0.06 (77)	0.095	0.167
S. Cromoglycate	0.79 (80)	0.97 (80)	0.18 (80)		

Study 1891 - ITT analysis

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	1.07 (90)	1.29 (88)	0.24 (88)		
NSO 2%	1.12 (89)	1.13 (87)	0.007 (87)	0.003	0.195
S. Cromoglycate	1.04 (89)	1.22 (89)	0.188 (89)	0.142	0.434

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.91 (90)	1.16 (88)	0.21 (88)		
NSO 2%	0.88 (89)	0.95 (87)	0.06 (87)	0.030	0.197
S. Cromoglycate	0.78 (89)	0.96 (89)	0.19 (89)	0.359	0.230

Study CR 1871 - Per protocol

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.78 (62)	1.42 (70)	0.68 (62)		
NSO 2%	0.50 (70)	0.93 (73)	0.45 (69)	0.019	0.0008

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.46 (63)	1.43 (70)	0.97 (63)		
NSO 2%	0.25 (69)	0.93 (73)	0.68 (68)	0.019	0.0005

Study CR 1871 - ITT

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.77 (64)	1.44 (72)	0.69 (64)		
NSO 2%	0.52 (73)	1.01 (76)	0.51 (72)	0.04	0.005

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.47 (65)	1.44 (72)	0.98 (65)		
NSO 2%	0.25 (72)	1.00 (77)	0.74 (72)	0.037	0.003

Study CR 1156 - Per protocol

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	1.28 (35)	1.23 (34)	-0.016 (34)		
NSO 2%	1.05 (39)	1.13 (39)	0.08 (39)	0.776	0.357

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.95 (35)	1.02 (34)	0.10 (34)		
NSO 2%	0.75 (39)	0.89 (39)	0.15 (39)	0.700	0.262

Study CR 1156 - ITT

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline

Placebo	1.25 (53)	1.34 (53)	0.084 (52)		
NSO 2%	1.12 (49)	1.15 (49)	0.038 (49)	0.575	0.185

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.93 (53)	1.10 (53)	0.16 (52)		
NSO 2%	0.78 (49)	0.86 (49)	0.08 (49)	0.443	0.096

Study CR 1242 - Per protocol

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.89 (46)	1.32 (47)	0.45 (46)		
NSO 2%	0.73 (46)	0.99 (47)	0.26 (46)	0.067	0.008

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.58 (46)	0.93 (47)	0.38 (46)		
NSO 2%	0.46 (46)	0.68 (47)	0.23 (46)	0.078	0.036

Study CR 1242 - ITT

Treatment	Mean score for itching			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.87 (55)	1.33 (56)	0.47 (54)		
NSO 2%	0.74 (56)	1.01 (57)	0.29 (55)	0.021	0.007

Treatment	Mean score for redness			Mann-Whitney U-test	
	Baseline	Peak period	Difference	Adjust Baseline	Not Adjust Baseline
Placebo	0.54 (55)	0.90 (56)	0.36 (54)		
NSO 2%	0.48 (56)	0.67 (57)	0.21 (55)	0.019	0.026

/S/

Qian Li, Sc.D
Mathematical Statistician

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Stan Lin, Ph.D
Team Leader