Medical Officer's Review of NDA 21-009
Amendment

NDA 21-009
Amendment

Submission Dates: 12/3/99 & 12/7/99
Receive Date: 12/6/99 & 12/8/99
Review Date: 12/8/99

Drug name:	ALOCRIL™
Generic name:	Nedocromil sodium ophthalmic solution
Chemical name:	4H-Pyrano[3,2-g] quinoline-2, 8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4, 6-dioxo-10-propyl-, disodium salt.
Sponsor:	Allergan, Inc. 2525 Dupont Drive, P.O. Box 19534 Irvine, CA 92623-9534 TEL (800) 347-4500, FAX (714) 246-4272
Pharmacologic Category:	Mast cell stabilizer
Proposed Indication(s):	For the treatment of ocular itch due to allergic conjunctivitis
Submitted:	Revised labeling

DRAFT
LABELING

4 pages

REDACTED

DRAFT

LABELING

Summary/Conclusions:

The labeling is acceptable. The application should be considered approvable from a clinical prospective.

/S/

Wiley A. Chambers, MD

Cc: Orig NDA 21-009
HFD-550
HFD-550/PM/Gorski
HFD-830/Chem/Tso
HFD-550/Pharm/Zoetis
HFD-880/Biopharm/Tandon
HFD-725/Stat/Li
HFD-550/MO/Dunbar
HFD-550/SMO/Chambers

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-009

NDA 21-009 Amendment	Submission Date:10/14/99 Receive Date: 10/15/99 Review Date: 11/30/99

Drug name:	Nedocromil Sodium 2% Ophthalmic Solution
Generic name:	Nedocromil Sodium ophthalmic solution
Chemical name:	4H-Pyrano[3,2-g] quinoline-2, 8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4, 6-dioxo-10-propyl-, disodium salt.
Sponsor:	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534 TEL (800) 347-4500 FAX (714) 246-4272
Pharmacologic Category:	Mast cell stabilizer
Proposed Indication(s):	For the prevention and treatment of ocular itch due to allergic conjunctivitis
Submitted:	10/14/99 Amendment with Allergan's response to the approvable letter dated October 1, 1999.

In the approvable letter dated 10/1/99 the agency raised the following three issues regarding NDA 21-009.

Issue One

The data submitted fails to support a claim for treatment of allergic conjunctivitis because there is insufficient information to support the treatment of redness. Please revise your proposed label to read "treatment of itching associated with allergic conjunctivitis" or provide additional information to support the claim of redness associated with allergic conjunctivitis.

Reviewer Comment: *Not acceptable. The sponsor responded with new labeling with an indication of "the prevention and treatment of ocular itch due to allergic conjunctivitis". A clean copy of the medical officer's response to this label is provided below.*

4 pages

REDACTED

DRAFT

LABELING

Issue Two

As requested in our fax communication of September 7, 1999, please provide all patient case report forms for the following clinical studies: 1170-1, 1170-2, 1343, 1344, 1871, 1156, 1891, 1242, 1959, and 1901.

Reviewer Comment: *The requested case report studies were provided. They were reviewed for suppression of data. The summary of this review is listed below.*

Study CR1170/1

NSO missing data	Reason	Data available	Case Report Form Reviewed	Placebo missing data	Reason	Data available	Case Report Form Reviewed
YA03	Never treated	None	Yes	YA07	Not given--pt not listed in sponsor's list of withdrawals: Presumed never treated in initial review. Review of case report forms shows patient received tx. Not clear why data was not included in electronic dataset.	None	Yes
YA28*	Nosebleed	Baseline & 7d tx	Yes	YA23*	Viral conjunctivitis: Sponsor states never treated	baseline & 1d tx	Yes
YA31	Never randomized	None	No	YA26*	Illness--asthma	Baseline & 7d tx	Yes
YA34	Never randomized	None	No	YA32	Never randomized	None	No
YB04*	Never treated	Baseline	Yes	YA33	Never randomized	None	No
YB09	Never treated	None	Yes	YB21*	Illness--asthma	Baseline & 1d tx	Yes
YB30	Never treated	None	Yes	YB32	Never randomized	None	No
YB31	Never randomized	None	No	YB33	Never randomized	None	No
YB34	Never randomized	None	No	YD03*	Illness--breast cancer	Baseline & 7d tx	Yes
				YD15	Never treated-bad labs	None	Yes
				YD22	Never treated-bad labs	None	Yes
				YD27	Never treated-bad labs	None	Yes

- Pt #04 started diary data but refused to continue the study prior to randomization because of needed concomitant medication which pt was unable to discontinue. Pt did not receive study drug.
- Patient YA07. Reason for not including data in electronic dataset from study 1170/1 was not given. Case report forms were not available for the initial medical officer review. It was presumed that the patient was never treated. Review of the case report forms shows that this patient was treated. The case report forms do not reveal why the data was not included by the sponsor. It is possible that the sponsor suppressed data in this case, or that the patient was overlooked.

Reviewer comment: *Review of the case report forms for study 1170/1 shows fair correlation between the electronic database and the case report forms. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study CR1170/2

NSO missing data	Reason	Data available	Case Report Form Reviewed	Placebo missing data	Reason	Data available	Case Report Form Reviewed
YC23	Non-compliance	baseline and 7d tx	Yes	YC06	Never treated	None	Yes
YC26	Never treated	None	Yes	YE15	Never treated	None	Yes
YE04	Drug Intolerance	baseline and 4d tx	Yes	YF14	Never treated	None	Yes
YE12	Never treated	None	Yes	YF33	Never treated	None	Yes
YE13	Never treated	None	Yes				
YF01	Never treated	None	Yes				
YF02	Never treated	None	Yes				
YF05	Diary Stolen	None	Yes				
YF21	Never treated	None	Yes				
YF30	Never treated	None	Yes				
YF34	Never treated	None	Yes				

- There is no evidence of data suppression in the case report forms reviewed.

Reviewer comment: *Review of the case report forms for study 1170/2 shows good correlation between the electronic database and the case report forms. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study CR1343

NSO missing data	Reason	Data available	Case Report Form Reviewed	Placebo missing data	Reason	Data available	Case Report Form Available
317	Itching, redness and swelling	baseline & 21d tx	Yes	None			
329	Never started tx	baseline	Yes				
332	Never started tx	baseline	?				

- Case report forms were reviewed for patient number 25. It is not clarified if this is the same patient randomized to #332 or not. Otherwise there is no evidence of data suppression in this study.

Reviewer comment: *Review of the case report forms for study 1170/2 shows good correlation between the electronic database and the case report forms. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study CR 1343

NSO missing data	Reason	Data available	Case Report Form Reviewed	Placebo missing data	Reason	Data available	Case Report Form Available
130	Never Randomized	None	No	325	Never Randomized	None	No
229	Never Randomized	None	No	326	Never Randomized	None	No
230	Never Randomized	None	No	327	Never Randomized	None	No
329	Never Randomized	None	No	328	Never Randomized	None	No
330	Never Randomized	None	No	224-31	Protocol violation	baseline & 28 d tx	Yes
530-6	Presumed Never Treated	baseline	No	312-8	Tx failure.	baseline & 21 d tx	Yes
426-10	Lost to follow up	baseline & 8d tx	Yes				
413-16	Illness-rhinitis	baseline & 10d tx	Yes				
225-32	Illness-sinus infection	baseline & 34 d tx	Yes				
315-19	Illness-URI	baseline & 26 d tx	Yes				
321-21	Illness-ophthalmic burns from disallowed eyedrop	baseline & 13 d tx	Yes				
522-18	Protocol violation-out of area	baseline & 36 d tx	Yes				

- Pt 530-06 case report forms not provided.
- Pt 522-18 the case report form duplicated data from 8/20 with two different itching scores. Otherwise the data matched that in the dataset.
- Pt 312-8 had case report forms which did not match the dataset data.

Reviewer comment: *Review of the case report forms for study 1343 shows good correlation between the electronic database and the case report forms. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study CR1959

NSO missing data	Reason	Data available	Case Report Form Reviewed	Placebo missing data	Reason	Data available	Case Report Form Reviewed
114	Never treated	None	Yes	430	?Never Treated	None	No
122	No show to appts (had drug x 5d)	None	Yes	418	Left study area	None	No
329	Not Randomized	None	No	529	Not Randomized	None	No
330	Not Randomized	None	No	719	Not Randomized	None	No
609	Left Study Area	None	Yes	1026	Swollen eye	baseline & 14 d tx	Yes
613	Pneumonia	None	Yes				
617	Nasal symptoms	Partial	Yes				
730	Not Randomized	None	No				
801	Intolerant to study drug	baseline & 14 d tx	Yes				
830	Not Randomized	None	No				
1006	Moved away from study area	Partial	Yes				
1029	Not Randomized	None	No				

- Patient 609 was left out of electronic database because patient left study area. The days the patient left the study area were during the preliminary period prior to

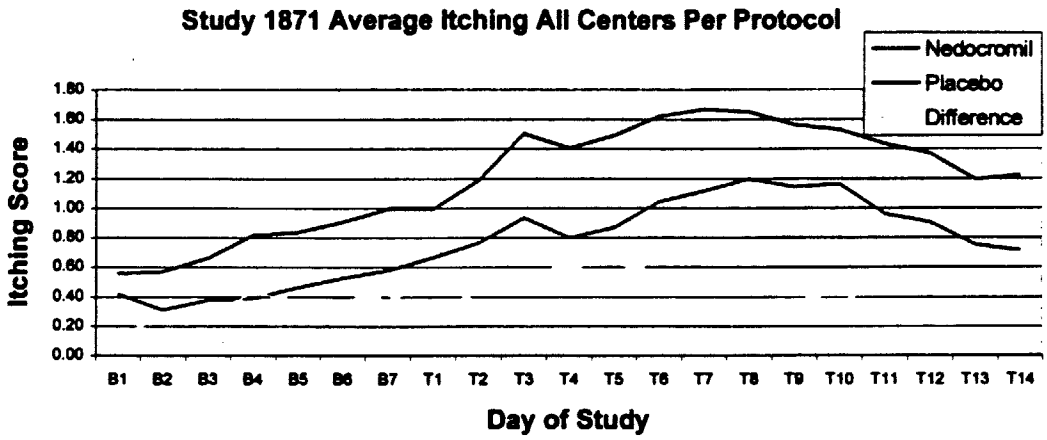
baseline. This would not effect the study. Pt had extensive diary card data and probably should have been included.

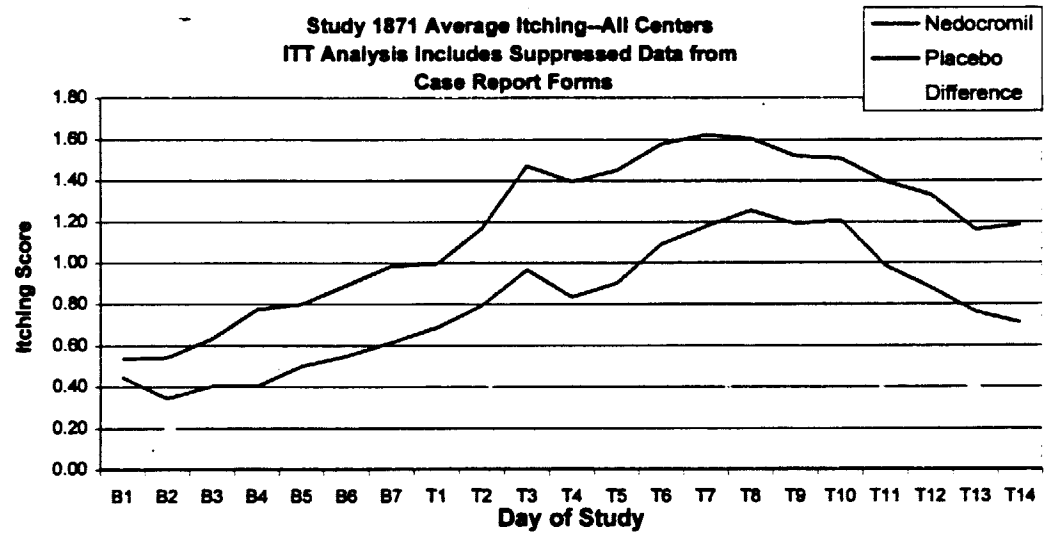
Reviewer comment: *Review of the case report forms for study 1959 shows good correlation between the electronic database and the case report forms. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study CR 1871

NSO missing data	Data available	Case Report Form Reviewed	Placebo missing data	Data available	Case Report Form Reviewed
97	None	Yes	227	baseline & 5 d tx	Yes
99	None	Yes			
159	2 d baseline	Yes			
183	baseline & 9 d tx	Yes			

- Patient 183 appeared to have data on the case report form that was left out of the electronic database. It is possible that data was suppressed. The case report diary form is in Swedish and translation is needed to clarify this. This patient violated protocol by taking steroids. The sponsor should have included all data for both ITT and Per protocol analysis.
- Patient 227 appeared to have data on the case report form that was left out of the electronic database. A withdrawal form seemed to indicate the patient was withdrawn because of poor cooperation. After the point where the sponsor did not included data in the electronic database the patient had written all zeros in the case report form. It is possible that data was suppressed, or that the zero entries indicated the poor cooperation.





Reviewer comment: *Review of the case report forms for study 1871 shows fair correlation between the electronic database and the case report forms. The above graphs illustrate that when the suppressed data is entered into an intent-to-treat analysis (second table) the result is similar to the per-protocol analysis conducted without the suppressed data. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study CR 1156

NSO missing data	Reason	Data available	Case Report Form Reviewed	Placebo missing data	Reason	Data available	Case Report Form Reviewed
3	Never Treated	None	Yes	5	Never Treated	None	Yes
43	Non cooperation	baseline & 7d tx	Yes	32	Never Treated	None	Yes
44	Never Treated	None	Yes	49	Never Randomized	None	No
48	Never Randomized	None	No	50	Never Randomized	None	No
51	Never Randomized	None	No	55	Never Randomized	None	No
52	Never Randomized	None	No	56	Never Randomized	None	No
53	Never Randomized	None	No	58	Never Randomized	None	No
54	Never Randomized	None	No	59	Never Randomized	None	No
57	Never Randomized	None	No	62	Never Randomized	None	No
60	Never Randomized	None	No	64	Never Randomized	None	No
61	Never Randomized	None	No	65	Never Randomized	None	No
63	Never Randomized	None	No	68	Never Randomized	None	No
66	Never Randomized	None	No	70	Never Randomized	None	No
67	Never Randomized	None	No	77	Presumed Never treated	None	No
72	Never Treated	None	No	94	Presumed Never treated	None	No
74	Never treated	None	No	71	Disallowed medication	Baseline & 9 d tx	Yes
97	Presumed Never treated	None	No	78	Disallowed medication	Baseline & 6 d tx	No
101	?	Baseline & 5 d tx	No	105	?	Baseline & 5 d tx	No
117							

- Patient 71 used oral prednisone, a disallowed treatment after nine days of treatment. Although additional diary card data was available, the sponsor did not include this data in the electronic database. The sponsor did suppress the data during the time the patient used oral prednisone.
- Patient 72 had no withdrawal form completed.
- Patient 101 had data listed in the electronic database for 5 days, then 11 days missing. The case report form shows data recorded for these days. A withdrawal form was not completed. It is not clear why data was missing here. There is possible data suppression.
- Patient 105 diary card was missing four days without data in the electronic database. It is not clear why.

Reviewer comment: *Review of the case report forms for study 1156 shows fair correlation between the electronic database and the case report forms. Even when data was suppressed, the sponsor failed to show efficacy. Thus, the suppression of data does not affect the decision for drug approval. Acceptable*

Study 1891

NSO Missing Data	Reason	Data Available	Case Report Form Available
331	Non Compliance- Never tx	None	Yes
380	Possibly Never Randomized	None	No
311	Lack of effect	Baseline & 6d tx	Yes
338	Lack of effect	Baseline	Yes
376	Lack of effect	Baseline & 7d tx	Yes
405	Suspected Adverse Rxn	1 day baseline	No
419	No explanation	Baseline & 9d tx	Yes
430	No explanation	Baseline & 9d tx	Yes
350	Lack of Effect	Baseline & 6d tx	Yes
Placebo Missing Data	Reason	Data available	Case Report
309	Lack of Effect	Baseline only	Yes
349	Lack of Effect	Baseline & 7d tx	Yes
441	Suspected Adverse Reaction	Baseline only	Yes
328	Wrong amount study drug	Baseline & 8d tx	Yes
Terfenadine missing data	Reason	Data Available	Case Report
209	Suspected Adverse Reaction	Baseline & 10 d tx	Yes
356	Lack of effect	Baseline & 9d tx	Yes
425	Severe Concurrent Illness	Baseline & 7d tx	Yes
434	Lack of effect	Baseline	Yes
413	Possible Missed Visit	Baseline & 10 d tx	Yes

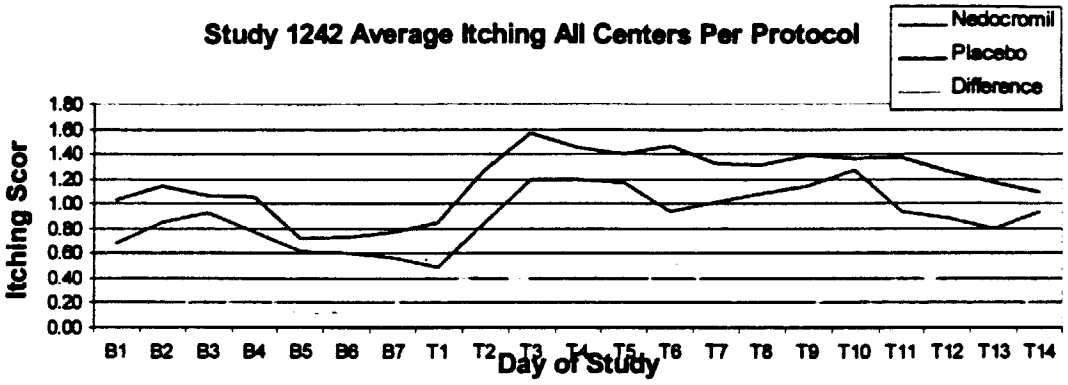
- Patients 209 and 430 had different values listed for the electronic database compared to the case report form.
- Patient 405 erroneously had the case report forms for patient 402 provided. The case report forms for patient 405 were not provided.
- Patient 356 and 209 terminated because of lack of effect of treatment. Systemic medication required. The termination date correlated with the systemic medication use. This also correlated with the missing data.

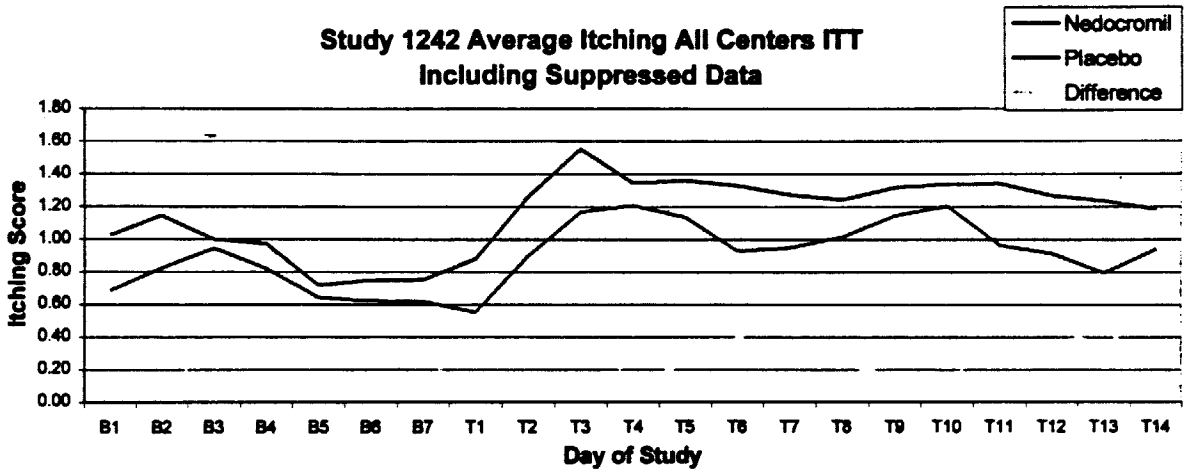
Reviewer comment: *Review of the case report forms for study 1891 shows fair correlation between the electronic database and the case report forms. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study 1242

NSO Missing Data	Reason	Data Available	Case Report Form Available	Placebo Missing Data	Reason	Data available	Case Report Form Available
21	Non-cooperation	None	Yes	17	Tx failure	BL & 9d tx	Yes
27	Non-cooperation	BL & 5d tx	Yes	31	Never Randomized	None	No
48	Never Randomized	None	No	35	Never Randomized	None	No
49	Never Randomized	None	No	40	Never Randomized	None	No
50	Never Randomized	None	No	46	Never Randomized	None	No
52	Never Randomized	None	No	51	Never Randomized	None	No
53	Never Randomized	None	No	57	Never Randomized	None	No
55	Never Randomized	None	No	59	Never Randomized	None	No
56	Never Randomized	None	No	60	Never Randomized	None	No
58	Never Randomized	None	No	70	Never Randomized	None	No
66	Never Randomized	None	No	78	Never Randomized	None	No
69	Never Randomized	None	No	89	Never Randomized	None	No
79	Never Randomized	None	No	90	Never Randomized	None	No
90	Never Randomized	None	No	94	Illness	None	Yes
88	Never Randomized	None	No	112	Non-cooperation & tx failure	BL & 12 d tx	Yes
97	x failure & adverse r	Baseline	Yes	121	Non-cooperation	BL & 9d tx	Yes
106	Tx failure	None	Yes	127	Non-cooperation	BL	Yes
113	Adverse rxn	None	Yes	128	Non-cooperation	None	Yes
114	Non-cooperation	None	Yes	140	Diary card missing	None	Yes
132	Diary card missing	None	Yes	141	Diary card missing	None	Yes
139	Non-cooperation	None	Yes	145	Left trial area 2d	BL & 7d tx	Yes
143	Non-cooperation	BL & 9d tx	Yes				

- Patient 27 lost the diary. No other data available.
- Patients 112 had different values listed for the electronic database compared to the case report form.
- Patients 132, 140, and 141 had missing diary cards.
- The available data for patient 106 included data when the patient was taking a disallowed medication.
- Patient 113 withdrew from the study prior to the baseline period.
- Patient 114 was left out of the electronic database because of contact lens use during the study. The patient was never formally withdrawn.
- Patient 139 had treatment failure. No diary cards were available in the CRF. Patient took Hismanal.
- Although patient 94 had diary card data listed in the case report form, the patient was completely left out of the electronic database because the patient took steroids for rhinitis during the study period.
- Patient 127 had two weeks of data listed on the case report form but only 1 week in the electronic dataset. Possible data suppression.
- Patient 145 had data suppressed for two days when the patient was outside the study area.
- Patient 128 did not "come to the control" per the withdrawal form. It is not clear what this means, but presumably the patient was noncompliant with study visits. There is no record that patient received the study drug.





Reviewer comment: *Review of the case report forms for study 1242 shows fair correlation between the electronic database and the case report forms. The above graphs illustrate that when the suppressed data is entered into an intent-to-treat analysis (second table) the result is similar to the per-protocol analysis conducted without the suppressed data. Where there is data discrepancy it is minimal, and does not effect the outcome of the study, or of the drug approval process. Acceptable.*

Study 1901

Reviewer Comment: *Medical officer review verifies that the case report forms were provided as requested. The sponsor failed to show efficacy in the summary provided in the original submission. Therefore, these were not reviewed in detail.*

Issue Three
Under 21CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

Reviewer Comment: *Acceptable. The sponsor submits copies of both 15 day adverse event reports submitted to the agency between March 1, 1998 and August 1, 1999. in this amendment, as well as a summary of the 10 non-serious adverse events reported. They were reviewed and do not alter the drug safety profile.*

/S/

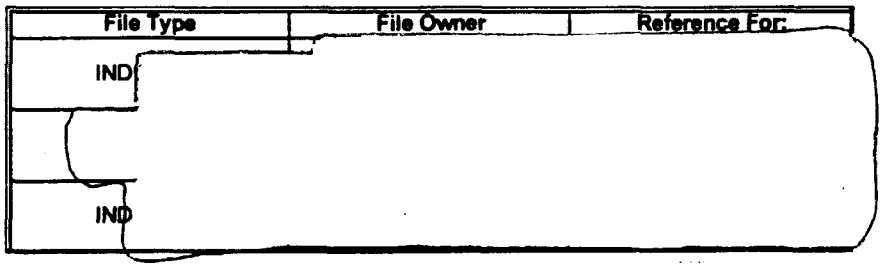
Jennifer A. Dunbar MD

Cc: Orig NDA 21-009
HFD-550
HFD-550/PM/Gorski
HFD-830/Chem/Tso
HFD-550/Pharm/Zoetis
HFD-880/Biopharm/Tandon
HFD-725/Stat/Li
HFD-550/MO/Dunbar
HFD-550/SMO/Chambers /S/ 12/1/99

Medical Officer's Review of NDA 21-009

NDA 21-009		Submission Date:	04/02/99
Original		Receive Date:	04/05/99
		Review Date:	09/28/99

Drug name:	Nedocromil Sodium 2% Ophthalmic Solution
Generic name:	Nedocromil Sodium ophthalmic solution
Chemical name:	4H-Pyrano[3,2-g] quinoline-2, 8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4, 6-dioxo-10-propyl-, disodium salt.
Sponsor:	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534 TEL (800) 347-4500 FAX (714) 246-4272
Pharmacologic Category:	Mast cell stabilizer
Proposed Indication(s):	Prevention and treatment of allergic conjunctivitis
Reviewer Comment:	*Not acceptable. The sponsor should choose one of the two terms, prevention or treatment.*
Dosage Form and Route of Administration:	Ophthalmic solution, Topical
NDA Drug Classification:	3P
Related Drugs:	Sodium Cromolyn Ophthalmic Solution Tilade (nedocromil sodium inhalation aerosol)
Submission:	Initial Submission
Related Submissions:	



2 Table of Contents

3 Material Reviewed

NDA 21-009: Volumes 1.1, 1.11-1.69

4 Chemistry/Manufacturing Controls-See Chemistry Review

Each mL contains: Active: Nedocromil sodium 20 mg (2%); **Preservative:** Benzalkonium chloride 0.01%; **Inactives:** Sodium Chloride 0.55% Edetate disodium 0.05% and purified water. It has a pH of 4.0 to 5.5.

Raw Material	Quantity mg/mL
Nedocromil	
Benzalkonium chloride	
Sodium chloride	
Purified Water	
Edetate disodium	

Additional Specifications:

pH	4.0 – 5.5
Osmolality	
Particle size	
Sterility	
Preservative efficacy	

Reviewer Comments: *No additional Chemistry Manufacturing Control issues identified from a clinical perspective.*

5 Animal Pharmacology/Toxicology-See Pharmacology & Toxicology Review

Reviewer Comments: *No additional animal Pharmacology/Toxicology issues identified from a clinical perspective.*

6 Clinical Background

Reviewer's Comments: *The product was originally developed and clinical studies conducted in support of the NDA by Fisons. Fisons was acquired by Rhone-Poulenc Rorer Pharmaceuticals Inc. The IND/NDA information and clinical studies were sold prior to NDA submission to Allergan.*

6.3 Foreign experience

Country	Date of Approval	Date of Launch
Australia	Sep-96	Marketing decision not to launch product
Austria	Feb-96	Apr-97
Canada	Jun-97	Aug-97
Denmark	Nov-94	Mar-95
Finland	Feb-95	Feb-95
France	1993	May-97
Germany	Sep-93	Mar-94
Greece	Nov-94	Oct-95
Holland	Sep-93	Mar-94
Italy	Nov-94	Mar-95
Ireland	Sep-95	1995
Mexico	Apr-96	Aug-96
New Zealand	May-95	Marketing decision not to launch product
Norway	Apr-95	Marketing decision not to launch product
Spain	Oct-95	Oct-95
Sweden	Apr-94	Jun-94
Switzerland	Aug-93	Mar-94
Poland	Dec-96	Unavailable
Portugal	Dec-95	Sep-97
United Kingdom	Mar-95	Apr-95

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Reviewer Comments: *No additional issues identified from a clinical perspective.*

7 Description of Clinical Data Sources (both IND and non-IND)

Thirty one trials were conducted and completed by or on behalf of Fisons/Allergan

Two dose-ranging studies were conducted.

STUDY #	SUBJECTS	SOLUTION %	DOSE	DESIGN
CP/HV 198/1	3 M / 3 F	0.5, 1.0,2.0,4.0	1 drop NSO* to one eye 1 drop vehicle to other eye	Ascending single dose
CP/HV 219	7 M / 5 F	1.0 & 2.0	1 drop NSO* to one eye 1 drop vehicle to other eye	Parallel group comparison: QID for 7 days

*=nedocromil sodium ophthalmic solution

The following tables summarize the ten studies evaluating the drug at the QID dosing level.

QID Studies in Allergic Conjunctivitis

STUDY #	LOCATION	CONDITION	NSO 2% PTS	VEHICLE PTS
CR 1333	Canada	SAC	73	68
CR 1284	Italy	SAC	101	55
CR 1111	England	SAC	32	32
CR 1318	England	SAC	28	12
CR 1756	England	SAC	42	42
CR 1557	France	SAC	29	29
CR 1225	Egypt	PAC	19	21
CR 1562	Belgium/Holland	PAC	20	23
CR 1698	Canada	PAC	34	30

BID v. QID Study in Allergic Conjunctivitis

STUDY #	LOCATION	CONDITION	NSO 2% PTS	VEHICLE PTS
CR 1423	France	PAC	BID 74, QID 73	73

Table of BID American Seasonal Allergic Conjunctivitis Studies

Review #	Protocol	Indication	Design	Treatment	# in each arm	Age Range	%(M/F)	Duration of treatment	Country Dates
1	CR1170/1	Allergic Conjunctivitis	Randomized Multicenter Double Masked Group-Comparative Placebo-Controlled Safety & Efficacy Environmental	Nedocromil Sodium 2%	43 Ne 2% 42 Placebo	13 to 60	(58/42)	8 weeks	USA 1986
2	CR1170/2	Allergic Conjunctivitis	Randomized Multicenter Double Masked Group-Comparative Placebo-Controlled Safety & Efficacy Environmental	Nedocromil Sodium 2%	52 Ne 2% 53 Placebo	12 to 67	(53/47)	8 weeks	USA 1986
3	CR1343	Allergic Conjunctivitis	Randomized Multicenter Double Masked Group-Comparative Placebo-Controlled Safety & Efficacy Environmental	Nedocromil Sodium 2%	58 Ne 2% 63 Placebo	12 to 61	(44/56)	8 weeks	USA 1987
4	CR1344	Allergic Conjunctivitis	Randomized Multicenter Double Masked Group-Comparative Placebo-Controlled Safety & Efficacy Environmental	Nedocromil Sodium 2%	69 Ne 2% 71 Placebo	12 to 62	(54/46)	8 weeks	USA 1987
5	CR1959	Allergic Conjunctivitis	Randomized Multicenter Double Masked Group-Comparative Placebo and Active Controlled Safety & Efficacy Environmental	Nedocromil Sodium 2%	116 Ne 2% 115 Opticrom 57 Placebo	13 to 65	(46/54)	8 weeks	USA 1989

Table of BID European and Canadian Seasonal Allergic Conjunctivitis Studies

Review #	Protocol	Indication	Design	Treatment	# in each arm	Age Range	%(M/F)	Duration of treatment	Country Dates
6	CR1871	Seasonal Allergic Conjunctivitis	Randomized Multicenter Double Blind Group-Comparative Placebo-Controlled Safety Efficacy Environmental	Nedocromil Sodium 2%	Ne 77 Pl 72	6 to 16	(62/38)	4 weeks	Sweden 1989
7	CR1156	Seasonal Allergic Conjunctivitis	Randomized Multicenter Double Blind Group-Comparative Placebo-Controlled Safety Efficacy Environmental	Nedocromil Sodium 2%	Ne 60 Pl 61	9 to 56	(32/68)	4 weeks	Canada 1986
8	CR1891	Seasonal Allergic Conjunctivitis	Randomized Multicenter Double Blind Group-Comparative Active & Placebo Controlled Safety Efficacy Environmental	Nedocromil Sodium 2% Terfenadine	Ne 89 Ter 89 Pl 90	12 to 68	(42/8)	4 weeks	Canada 1989
9	CR1242	Seasonal Allergic Conjunctivitis	Randomized Multicenter Double Blind Group-Comparative Placebo-Controlled Safety Efficacy Environmental	Nedocromil Sodium 2%	Ne 64 Pl 62	7 to 60	(33/67)	4 weeks	Finland 1987
10	CR 1901	Seasonal Allergic Conjunctivitis	Randomized Multicenter Double Blind Group-Comparative Placebo and Active Controlled Safety Efficacy Environmental	Nedocromil Sodium 2%	Ne 60 Cr 61 Pl 64	12 to 55	(39/61)	4 weeks	Finland 1989

Clinical Studies In Other Indications And Additional Information

Ten studies were conducted in indications other than allergic conjunctivitis. The following tables present a summary of the results of these studies.

Summary of Other Therapeutic Trials

Study No.	Country	No. Pts. In Efficacy Analysis	Age Range Sex	Design/Population	Dosage Duration	Results
Giant Papillary Conjunctivitis (GPC)						
CR 1957 (88-52)	USA	36-NSO 2% 37-Vehicle	12-61 21M/52F	6 centers, double-blind, vehicle-controlled, group comparative: Patients with symptomatic contact lens-associated GPC, who continue to wear contact lenses.	1 drop/eye bid 4 weeks	No statistically significant differences between treatment groups.
CR 1624 (88-10)	USA	56-NSO 2% 55-Vehicle	15-66 39M/72F	6 centers, double-blind, vehicle-controlled, group comparative: Patients with symptomatic contact lens-associated GPC, who continue to wear contact lenses.	1 drop/eye bid 4 weeks	Measurements of overall eye condition, itchy eyes, and tolerance of lenses. No statistically significant differences between treatment groups in these variables or in the clinician and patient's opinions of effectiveness.
CR 1368	England	22-NSO 2% 23-Vehicle	18-71 15M/30F	1 center, double-blind, vehicle-controlled, group comparative: Patients with contact lens-associated GPC, who have symptoms severe enough to require treatment but who can continue to wear their contact lenses.	1 drop/eye bid 6 weeks	Statistically significant difference in favor of NSO 2% in a limited number of the parameters measured
Vernal Keratoconjunctivitis (VKC)						
CR 1240 (SD1401/1/A)	Egypt	48-NSO2% 48-Opticrom 42-Vehicle	3-36 99M/38F 1 unknown	1 center, double-blind, vehicle-controlled, group comparative: Patients with bilateral VKC, who are in the acute phase of the disease.	1 drop/eye qid 4 weeks	Trends in favor of NSO 2% over vehicle were seen for patient diary card symptoms and the clinician's assessment of symptoms at each time point.
CR 1214 (SD CR 1214/A)	Egypt	17-NSO 2% 19-Vehicle	3-40 28M/8F	1 center, double-blind, vehicle-controlled, group comparative: Patients with bilateral VKC, who are in the acute phase of the disease.	1 drop/eye qid 4 weeks	Statistically significant difference in favor of NSO 2% in a limited number of the parameters measured.
CR 1290 (SD 11348/A)	Israel	64-NSO 2% 65-Vehicle	4-32 88M/41F	1 center, double-blind, vehicle-controlled, group comparative: Patients with bilateral VKC, who are in the acute phase of the disease.	1 drop/eye qid 12 weeks	Statistically significant difference in favor of NSO 2% in a limited number of the parameters measured. There was no difference between groups with respect to eye symptoms.

CR 1182 (SD 11400/1/A)	South Africa	15-NSO 2% 18-Vehicle	3-21 21M/12F	1 center, double-blind, vehicle-controlled, group comparative: Patients with bilateral VKC, who are in the acute phase of the disease and receiving topical steroids.	1 drop/eye qid 4 weeks	There were no clinically relevant effects of NSO 2% in this study largely due to the continued use of symptom-suppressing topical steroids in both treatment groups
CR 1394 (SD CR1394/A)	Italy	8-NSO 2% 11-Vehicle	7-32 14M/5F	1 center, double-blind, vehicle-controlled, group comparative: Patients with active, severe VKC.	1 drop/eye qid 6 weeks	Statistically significant difference in favor of NSO 2% in a limited number of the parameters measured.
Trachoma						
CR 1241 (SD CR1218/A)	Egypt	31-NSO 2% 32-Vehicle	9-60 25M/38F	1 center, double-blind, vehicle-controlled, group comparative: Patients with stage 1 or 2 active trachoma.	1 drop/eye qid 8 weeks	NSO 2% may reduce discomfort associated with trachoma, although no evidence for efficacy in the therapeutic management of trachoma was seen.
Blepharitis						
CR 1218 (SD CR1218/A)	England	32-NSO 2% 23-Vehicle	14-80 24M/31F	2 centers, double-blind, vehicle-controlled, group comparative: Patients with a history of chronic or recurrent blepharitis over the past 2 years, who currently have active blepharitis or blepharo-conjunctivitis that is not grossly purulent	1 drop/eyelid qid 4 weeks	This study provided no evidence that NSO 2% had any therapeutic benefit over vehicle in the treatment of blepharitis.

7.1.1 Study #1 Protocol #CR1170/1

Title: A Multicenter Double-Blind Group Comparative Study of the Efficacy and Safety of Nedocromil Sodium 2% Ophthalmic Solution in the Treatment of Ragweed Seasonal Allergic Conjunctivitis

Objectives: To evaluate the safety and efficacy of 2% nedocromil sodium solution in the treatment of seasonal allergic conjunctivitis caused by ragweed pollen.

Study design: A double-masked, vehicle controlled, randomized study in which, after a 1 week baseline period, patients were treated with the study drug (Active or Vehicle) BID for 8 weeks.

Study duration: August to October 1986

Drug Schedule: Dosing was a single drop in both eyes delivered twice daily for 8 weeks

Table of Investigators and Study Centers:

Investigator	Address	City, State	Number Randomized	Number Completed
S. Roget Hirsch, M.D.	5810 West Oklahoma Avenue	Milwaukee, WI 53219	34	29
Julian Melamed, M.D.	6 Tyngsboro Road	Westford, MA 01886	30	25
Robert Schwartz, M.D.	919 Westfall Road	Rochester, NY 14168	30	26
		Total	94	80

Study Plan: The baseline period was planned to coincide to the start of the ragweed season. The treatment period was timed to encompass the period of peak ragweed pollen. The focus of the study was the 2-3 week period with highest pollen counts. Patients recorded symptoms on diary cards for 9 weeks and a clinic assessment occurred 7 times. An ophthalmic exam was performed at baseline, after 1 week of treatment and at conclusion for safety assessment.

Active drug solution:	
Nedocromil sodium	2.00%
Benzalkonium chloride (BKC)	0.01%
Edetate disodium (EDTA)	0.05%
NaCl	0.55%
Purified water	qs

Reviewer Comment: *The exact identity of the vehicle solution was not provided.*

Masking: The study was conducted double-masked. All bottles of study medication were pre-coded by the sponsor, and supplied to the investigator. As patients entered the study, the investigator assigned the patient to the next sequential study code number available. The investigator was provided with a set of sealed envelopes containing the code to be opened only in the event of an emergency.

Concomitant Medication:

Permitted:

- Artificial tears.
- Topical medication (Nasalide®) for rhinitis symptoms.

Not Permitted:

- All other medication

Number of subjects (planned and analyzed):

	Sponsor Analysis			Medical Officer Analysis		
	NSO 2%	Placebo	Total	NSO 2%	Placebo	Total
Planned			125			125
Pts randomized to treatment	47	47	94	47	47	94
Pts who began treatment	43	43	86	43	43	86
Pts who completed study				42	38	80
Withdrawals				1	5	6
Treatment failure				0	0	0
Dropout due to AE				1	1	2
Other Dropouts				0	4	4
Analyzed: Efficacy	43	42	85	42	40	82
Analyzed: Safety	43	43	86	43	43	86

Table Accounting for Missing Data:

NSO missing data	Reason	Data available	Case Report Form Available	Placebo missing data	Reason	Data available	Case Report Form Available
YA03	Never treated	None		YA07	Not given–pt not listed in sponsor's list of withdrawals: Presumed never treated	None	
YA28*	Nosebleed	Baseline & 7d tx	Yes	YA23*	Viral conjunctivitis: Sponsor states never treated	baseline & 1d tx	
YA31	Never randomized	None		YA26*	Illness–asthma	Baseline & 7d tx	Yes
YA34	Never randomized	None		YA32	Never randomized	None	
YB04*	Never treated	Baseline		YA33	Never randomized	None	
YB09	Never treated	None		YB21*	Illness–asthma	Baseline & 1d tx	Yes
YB30	Never treated	None		YB32	Never randomized	None	
YB31	Never randomized	None		YB33	Never randomized	None	
YB34	Never randomized	None		YD03*	Illness–breast cancer	Baseline & 7d tx	Yes
				YD15	Never treated-bad labs	None	
				YD22	Never treated-bad labs	None	
				YD27	Never treated-bad labs	None	

*Patient for which partial data is available

Gray shading indicates that a patient was excluded from the medical officer analysis.

Reviewer Comment: *Not acceptable. The sponsor does not account for patient YA07. Otherwise review of case report forms of patients with partial data shows no data suppression by the sponsor.*

Demographics:

Subjects		Nedocromil	% Nedocromil	Placebo	% Placebo
Gender	Female	21	49%	15	36%
	Male	22	51%	27	64%
Mean Age (Years)		33.3		31.1	

Reviewer Comment: *Not acceptable. Patient race and iris color were not provided.*

Study Flow Chart

Procedure	Visit 1 Day -1	Visit 2 Day -7	Visit 3 Day 0	Visit 4 Day 7	Visit 5 Day 21	Visit 6 Day 35	Visit 7 Day 56
Randomization	X						
Screening	X						
Start baseline		X					
End baseline			X				
Collection of blood	X						
Collection of urine	X						
Record of AE		X	X	X	X	X	X
External exam				X	X	X	X
Slit Lamp exam				X	X	X	X
Conjunctival injection				X	X	X	X
Conjunctival edema				X	X	X	X
Limbal injection				X	X	X	X
Limbal edema				X	X	X	X
Monitor Diary - Compliance				X	X	X	X

Subject Population Patients had a history of seasonal allergic conjunctivitis, demonstrated a positive skin test to ragweed antigen, and met the inclusion and exclusion criteria.

Inclusion Criteria

- Healthy male, or healthy female of non-childbearing potential, between the ages of 12 and 65, inclusive.
- History of seasonal allergic conjunctivitis requiring continuous treatment during the ragweed pollen season of at least the two previous years (1984 & 1985).
- A positive skin test of at least 2+ to ragweed.
- Patients on immunotherapy known to develop symptoms of ragweed-sensitive allergic conjunctivitis and not receiving immunotherapy since the last ragweed season.
- Patients willing and able to remain in the same area during the trial.
- Patients willing and able to comply with trial procedures and give informed consent.
- Patients with no clinically significant abnormal laboratory values.
- Patients with no clinically significant abnormalities except asthma on physical exam.

Exclusion Criteria

- Patients who were asymptomatic or mildly or sporadically symptomatic during the last ragweed pollen season.
- Patients who received no medications to control their symptoms during the previous two ragweed seasons.
- Patients with a history suggestive of perennial conjunctivitis with little or no seasonal flare-up.
- Patients with additional pathology as a cause for their conjunctivitis symptoms.
- Patients with vernal keratoconjunctivitis or other forms of conjunctivitis.
- Patients who used topical (ocular) or oral corticosteroids, Nasalcrom, or Opticrom within two weeks of starting the baseline or who are receiving decongestants, vasoconstrictors, or theophylline.
- Patients with a known hypersensitivity to nedocromil sodium, benzalkonium chloride or edetate disodium.
- Patients with a history of chronic use of topical decongestants.
- Patients who wear contact lenses unless they agree in writing not to wear their lenses for the study duration.
- Patients *with* diagnosed cataracts or ocular hypertension in either eye.
- Patients who have had a corneal transplant in either eye.

Reviewer Comment: *Acceptable.*

Criteria for evaluation:

Efficacy:

Diary cards were kept with individual scores recorded for itchy eyes, burning eyes, tearing eyes and overall eye condition.

The four symptoms were assessed daily by the patient on the following five-point scale:

0 = none: symptom absent
1 = mild: symptom barely noticeable
2 = moderate: symptom caused some discomfort
3 = severe: symptom caused much discomfort without interfering with daily routine
4 = very severe: symptom present for most of the day. Caused enough discomfort to interfere with daily routine.

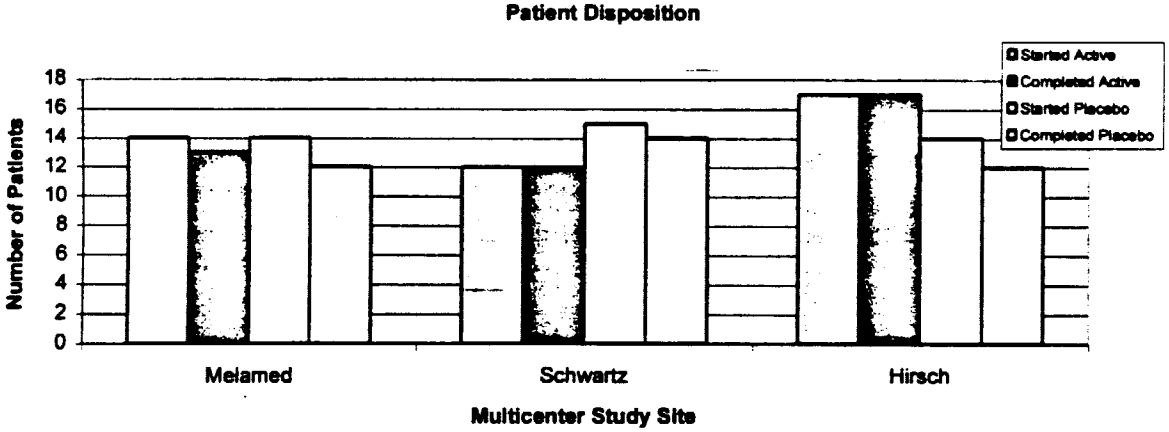
Primary efficacy variable:

"Summary score:" This is defined as the sum of the individual symptom scores for itchy eyes, burning eyes, tearing eyes, and overall eye condition enumerated above.

Secondary outcome variables:

- Clinician assessment at each clinic visit of itchy eyes, burning eyes, tearing eyes, and overall eye condition.
- Clinician review of the interval patient diary records for itchy eyes, burning eyes, tearing eyes, and overall eye condition.
- Clinician's overall opinion of treatment effectiveness.
- Patient's overall opinion of treatment effectiveness.

Disposition:



Reviewer Comment: *Acceptable. Similar numbers of patients started and completed the active and vehicle groups. Each investigator contributed similarly to these groups.*

Withdrawals and Exclusions: Patients were withdrawn from the study for the following reasons:

- Evidence of intolerance to the test medication
- Illness making discontinuation from the study necessary
- Documented non-compliance for failure to maintain the daily diaries
- Erratic use of the study drug
- Failure to appear for scheduled clinic visits
- The use of concomitant medications not prescribed by the investigator
- Loss to follow-up
- Movement out of the study area
- The patient may withdraw consent for personal reasons at any time.

Table of Patient Withdrawals and Exclusions After Randomization

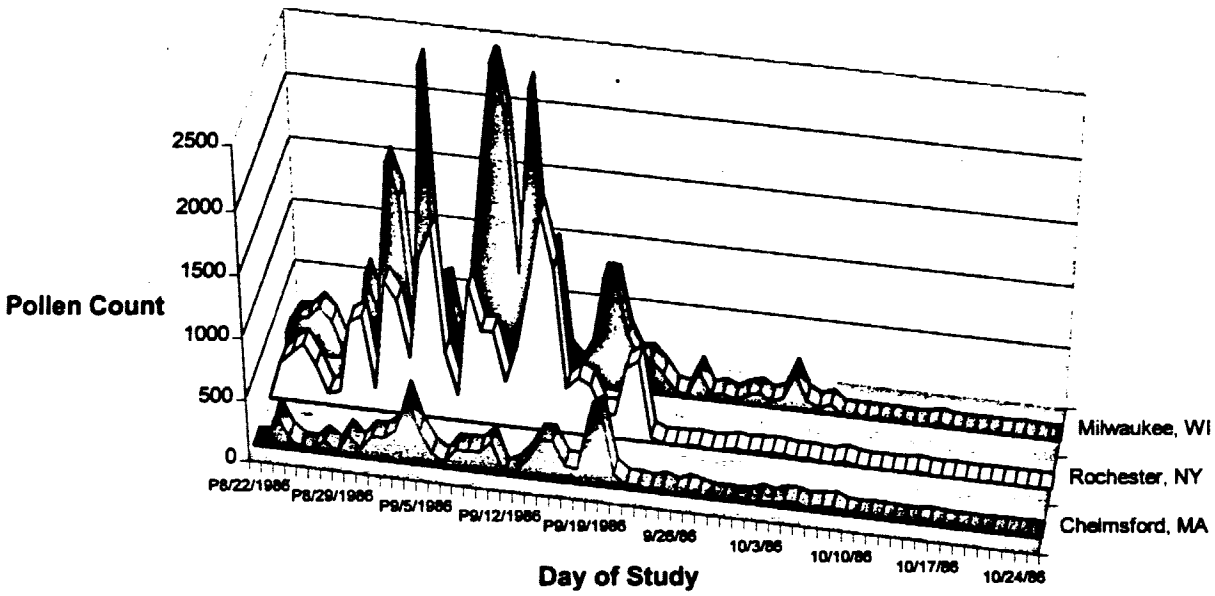
Pt No	Sex	Age	Duration of Treatment	Reason	Treatment	Clinic	Excluded Analysis
YA03	M	20	0 days *	Protocol violation - non compliance	Nedocromil	Melamed	Efficacy Safety
YA28	M	25	7 days	Severe sneezing, nosebleeds	Nedocromil	Melamed	Diary
YA07	?	?	?	Sponsor did not provide a reason	Placebo	Melamed	Diary
YA16	M	38	12 days	Intercurrent illness - burning eyes and nose with use of study drug (Pt d/c drug use)	Placebo	Melamed	Included
YA23	M	24	0 days *	Intercurrent illness - viral syndrome with viral conjunctivitis	Placebo	Melamed	Efficacy Safety
YA26	M	31	7 days	Intercurrent illness - increased asthma symptoms	Placebo	Melamed	Diary
YB04	M	13	0 days *	Mother started new job. Unable to make visits.	Nedocromil	Schwartz	Efficacy Safety
YB09	F	37	0 days *	Missed initial eye exam.	Nedocromil	Schwartz	Efficacy Safety
YB30	M	22	0 days *	Time constraints of new job. Unable to make visits	Nedocromil	Schwartz	Efficacy Safety
YB21	F	31	2 days	Increased allergy symptoms triggered asthma; required disallowed medications	Placebo	Schwartz	All Efficacy Analysis
YD03	F	27	7 days	Intercurrent illness - breast cancer	Placebo	Hirsch	Diary
YD15	NA	NA	0 days *	Abnormal laboratory results. Was not entered into baseline.	Placebo	Hirsch	Efficacy Safety
YD22	NA	NA	0 days *	Abnormal laboratory results. Was not entered into baseline.	Placebo	Hirsch	Efficacy Safety
YD27	NA	NA	0 days *	Abnormal laboratory results. Was not entered into baseline.	Placebo	Hirsch	Efficacy Safety

* Never began study medication

Reviewer Comment: *Not acceptable. No data was provided for vehicle patient YA07; the sponsor did not specify why. Available data from patients who withdrew from the study were included by the sponsor in the analysis as long as the recorded scores for at least half (11 or more) of the days of the peak pollen period. Eight patients withdrew from the study prior to receiving study medication. Four of eighty-three (4.8%) patients were excluded: 1 Nedocromil and 3 Vehicle failed to receive study drug for at least half of the peak pollen period. The reason for the exclusions is given in the table above. No patients were withdrawn due to treatment failure.*

Efficacy:

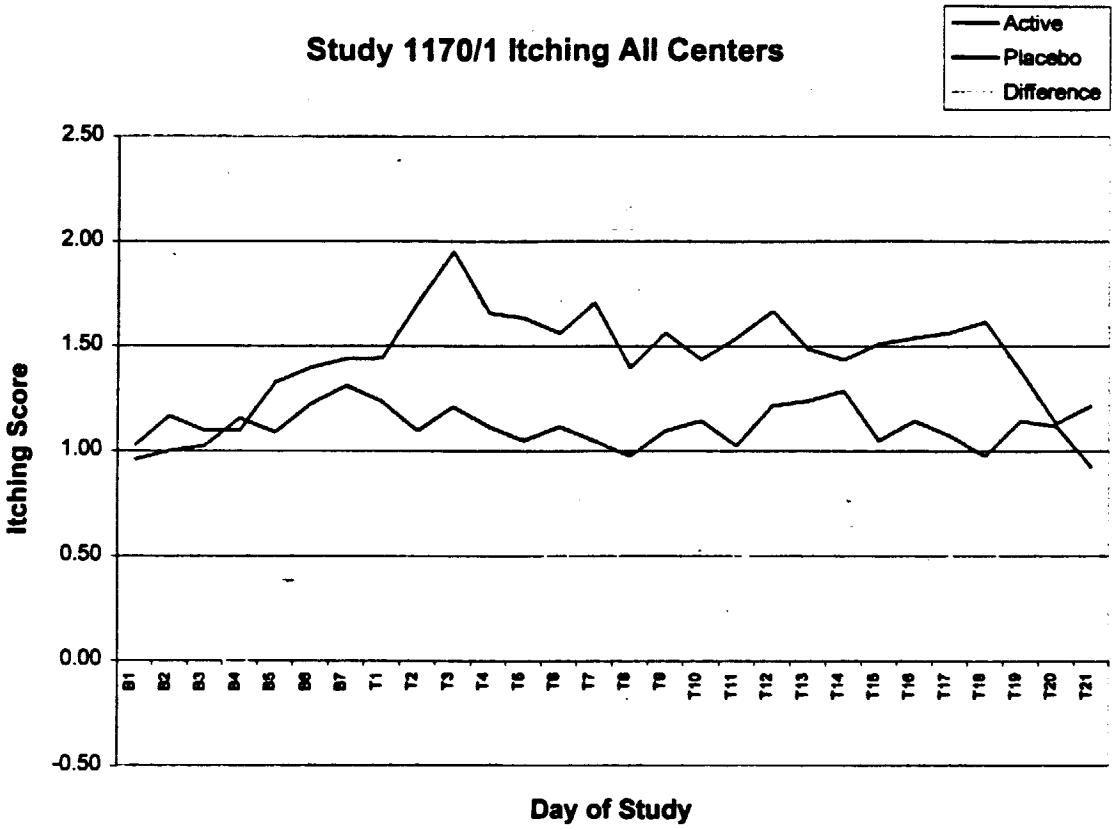
Study 1170/1 Pollen Count by Study Center

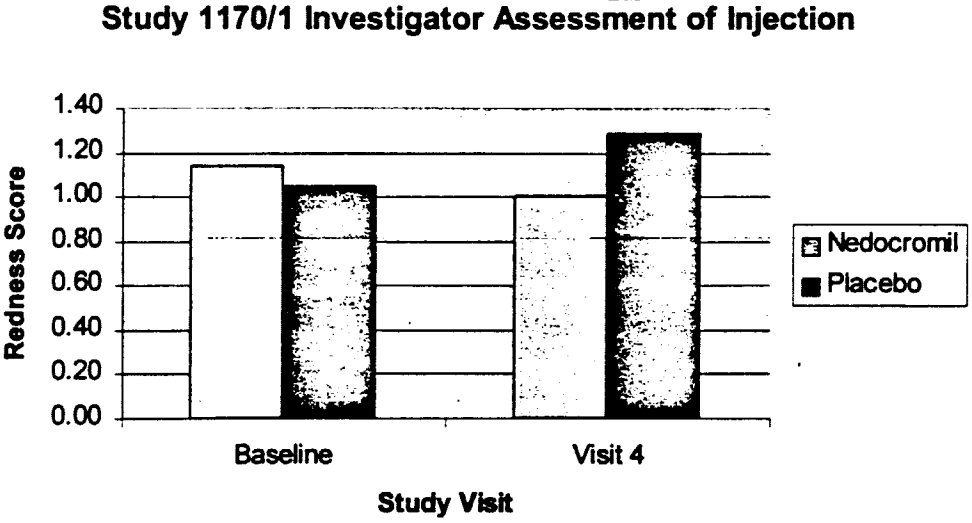


The magnitude of the pollen counts was least in Chelmsford, MA (Dr. Melamed), followed by Rochester, NY (Dr. Schwartz), and was greatest in Milwaukee, WI (Dr. Hirsch). For purposes of the sponsor analysis, the 21-day period from August 22, 1986 to September 11, 1986 inclusive was designated by the sponsor as the peak pollen period for all clinics. These days correspond with the first three weeks of treatment with the test medication. Treatment for all patients began within one day of August 21, 1986.

Reviewer Comment: *Acceptable. The raw pollen count data provided has justified the choice of the peak pollen period.*

Location	Sponsor Peak Pollen Period	Mean Pollen Count	Start Treatment	Minimum # of Days before Peak Pollen season	# of Patients	Medical Officer Peak Pollen Period	Medical Officer baseline Period
Chelmsford	8/22 to 9/11	180	8/21 +/- 1 day	0	29	8/22 to 9/11	8/15 to 8/21
Rochester	8/22 to 9/11	630	8/21 +/- 1 day	0	29	8/22 to 9/11	8/15 to 8/21
Milwaukee	8/22 to 9/11	825	8/21 +/- 1 day	0	31	8/22 to 9/11	8/15 to 8/21





Statistical Analysis of Study 1170/1

Study 1170/1	Mean score for itching					Koch's p-value (2-sided)	Mann-Whitney p-value		Difference
Tx	Baseline	# Pts	Peak Period	# Pts	Difference		Adjust baseline	Not adjust baseline	
Placebo	1.18	40	1.51	40	0.33				
Nedocromil	1.14	42	1.09	42	-0.05	0.001	0.003	0.002	0.42
Study 1170/1	Mean score for redness by investigator					Koch's p-value (2-sided)	Mann-Whitney p-value		Difference
Tx	Baseline	# Pts	Peak Period	# Pts	Difference		Adjust baseline	Not adjust baseline	
Placebo	1.05	42	1.29	42	0.23				
Nedocromil	1.14	43	1	43	-0.14	0.038	0.016	0.038	0.29

Reviewer Comment: *Acceptable. The graph shows similarity between the Nedocromil and Vehicle groups during the baseline period with a clear separation between the two groups during the 21-day treatment period. The statistical analysis above also supports the claim that Nedocromil is efficacious in treating the itching associated with seasonal allergic conjunctivitis.*

Adverse Events:

Preferred Term	Active	Active %	Placebo	Placebo %
Eye burning	8	19%	9	21%
Taste perversion	9	21%	0	0%
Eye itching	1	2%	3	7%
Eye irritation	3	7%	0	0%
Headache	2	5%	1	2%
Eye grittiness	2	5%	0	0%
Eye redness	2	5%	0	0%
Eye stinging	1	2%	1	2%
Eye dryness	1	2%	1	2%
Nose burning	2	5%	2	5%
Eye watering	0	0%	2	5%
Eye soreness	0	0%	2	5%
Sinusitis	0	0%	2	5%
Migraine	1	2%	0	0%
Neuralgia	2	5%	0	0%
Blindness -night	1	2%	0	0%
Photophobia	2	5%	0	0%
Earache	1	2%	0	0%
Dyspepsia	1	2%	0	0%
Nose soreness	1	2%	0	0%
Application site reaction	0	0%	1	2%
Vision abnormal	0	0%	1	2%
Smell perversion	0	0%	1	2%
Fever	0	0%	1	2%
Nose itching	0	0%	1	2%
Nose running	0	0%	1	2%

Reviewer Comment: *Adverse events occurring at >5% incidence, including burning, taste perversion, itching, irritation, headache, grittiness, redness, burning, neuralgia, and photophobia will be reported in the label.*

7.1.2 Study #2 Protocol #CR1170/2

Title: A Multicenter Double-Blind Group Comparative Study of the Efficacy and Safety of Nedocromil Sodium 2% Ophthalmic Solution in the Treatment of Ragweed Seasonal Allergic Conjunctivitis

Objectives, Study design, Drug Schedule, Study Plan, Masking, Concomitant Medication, Study Flow Chart, Subject Population, Inclusion Criteria, Exclusion Criteria, Criteria for evaluation, and Reasons for Withdrawals and Exclusions: Same as Study CR 1170/1

Reviewer Comment: *Acceptable.*

Study duration: Late summer to early autumn 1986

Table of Investigators:

Investigator	Address	City	Country	Number Randomized	Number Completed	Total
Malcolm Blumenthal, M.D.	42 Delaware St SE	Minneapolis, MN 55455	USA	34	29	63
Donald Aaronson, M.D.	Suite #301	Des Plaines, IL 60016	USA	16	12	28
William Silvers, M.D.	7180 E. Orchard Road	Englewood, CO 80111	USA	33	32	65
Howard Zeitz, M.D.	[redacted] of Chicago 550 West Webster	Chicago, IL 60614	USA	34	25	59
			Total	117	98	215

Number of subjects (planned and analyzed):

	Sponsor Analysis			Medical Officer Analysis		
	NSO2%	Placebo	Total	NSO2%	Placebo	Total
Planned						
Pts randomized to treatment				60	57	117
Pts who began treatment				52	53	105
Pts who completed study				47	51	98
Withdrawals				5	2	7
Treatment failure				0	0	0
Dropout due to AE				4	0	4
Other Dropouts				1	2	3
Analyzed: Efficacy	49	53	102	50	53	102
Analyzed: Safety	52	53	105	52	53	105

Demographics:

Subjects		Nedocromil	% Nedocromil	Placebo	% Placebo
Gender	Female	25	49%	24	45%
	Male	26	51%	29	55%
Mean Age (Years)		33.5		31	

Reviewer Comment: *Not acceptable. Patient race and iris color were not provided.*

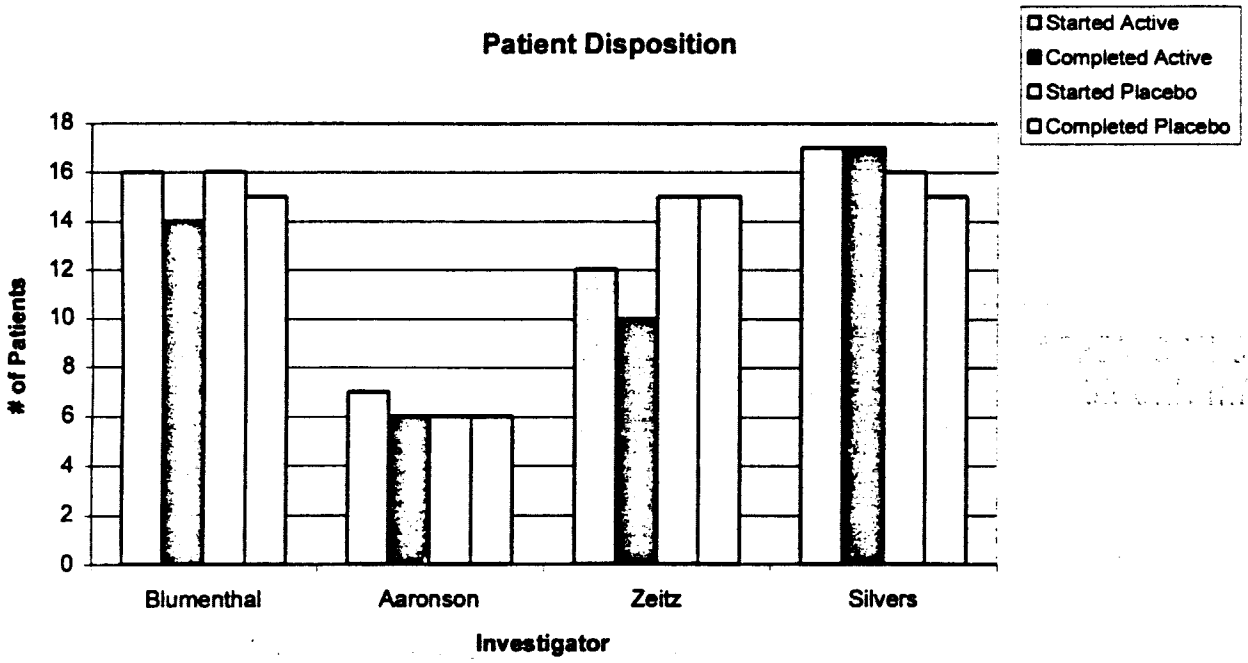
Table Accounting for Missing Data:

NSO missing data	Reason	Data available	Case Report Form Available	Placebo missing data	Reason	Data available	Case Report Form Available
YC23	Non-compliance	baseline and 7d tx	No	YC06	Never treated	None	
YC26	Never treated	None		YE15	Never treated	None	
YE04	Drug Intolerance	baseline and 4d tx	Yes	YF14	Never treated	None	
YE12	Never treated	None		YF33	Never treated	None	
YE13	Never treated	None					
YF01	Never treated	None					
YF02	Never treated	None					
YF05	Diary Stolen	None	No				
YF21	Never treated	None					
YF30	Never treated	None					
YF34	Never treated	None					

Gray shading indicates that a patient was excluded from the medical officer analysis.

Reviewer Comment: *Not Acceptable. Although diary card data is recorded for patient YE04 in the case report form it is not listed in the electronic data set.*

Disposition:



Reviewer Comment: *Acceptable. Each investigator contributes similarly to the number of patients and patient withdrawals. A similar number of patients started and completed the Active and Vehicle groups.*

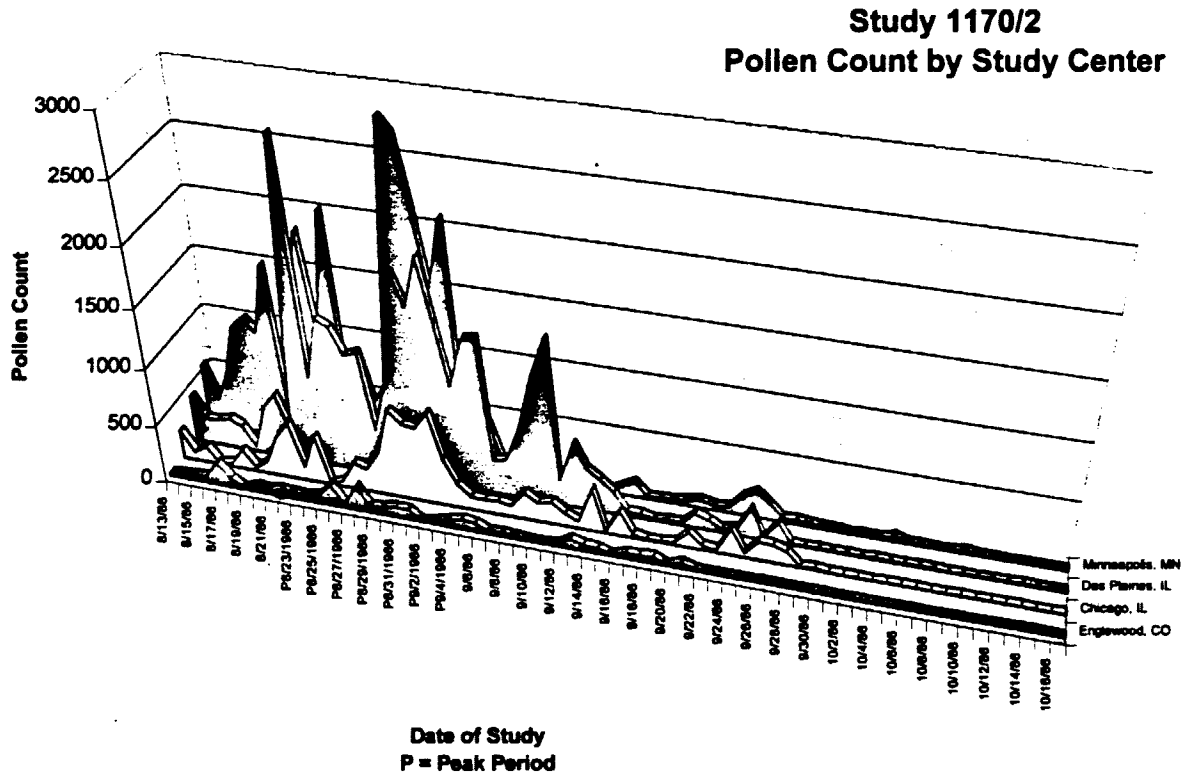
Table of Withdrawals, Exclusions, and Protocol Deviations After Randomization

Pt No	Sex	Age	Duration of Treatment	Reason	Treatment	Clinic	Excluded Analysis
YC17	M	30	34 days	Abnormal lab results after repeated testing	Active	Blumenthal	None
YC23	M	65	8 days	Non-compliance. Patient left office and would not return after waiting a long time to be seen	Active	Blumenthal	Efficacy
YC26	F	25	0 days*	Non-compliance. Patient did not have sufficient time for study.	Active	Blumenthal	Efficacy Safety
YC06	M	34	0 days*	Non-compliance. Patient did not return and could not be contacted.	Placebo	Blumenthal	Efficacy Safety
YC20	F	45	25 days	Non-compliance. Personal reasons. Patient left area.	Placebo	Blumenthal	None
YE04	M	19	4 days	Intolerance to study drug	Active	Aaronson	Efficacy
YE12	F	45	0 days*	Non-compliance. Patient could not comply with ophthalmic examinations	Active	Aaronson	Efficacy Safety
YE13	F	37	0 days*	Non-compliance. Patient objected to visit schedule and to taking eye drops.	Active	Aaronson	Efficacy Safety
YE15	F	27	0 days*	Non-compliance. Patient could not keep ophthalmic examination appointments.	Placebo	Aaronson	Efficacy Safety
YF01	M	34	0 days*	Abnormal results at screening eye examination.	Active	Zeitz	Efficacy Safety
YF02	M	41	0 days*	Abnormal baseline lab results after repeated testing.	Active	Zeitz	Efficacy Safety
YF05	M	33	21 days	Non-compliance. Patient withdrew after contents of his car (including study medication and diary card) were stolen	Active	Zeitz	Efficacy
YF11	M	26	40 days	Other illness. Injury to eye while at work.	Active	Zeitz	None
YF21	M	29	0 days*	Abnormal results at screening eye examination	Active	Zeitz	Efficacy Safety
YF30	F	30	0 days*	Non-compliance. Patient did not wish to continue.	Active	Zeitz	Efficacy Safety
YF34	F	26	0 days*	Non-compliance. Patient did not wish to continue.	Active	Zeitz	Efficacy Safety
YF14	M	58	0 days*	Abnormal results at screening eye examination.	Placebo	Zeitz	Efficacy Safety
YF33	M	21	0 days*	Non-compliance. Patient unable to keep appointments	Placebo	Zeitz	Efficacy Safety
YG13	F	67	37 days	Protocol violation. Age limit was 65 years.	Placebo	Silvers	None

* Never began study medication

Reviewer Comment:. *Acceptable. Of the 15 patients excluded from the study, twelve never received treatment. Three nedocromil patients of 102 (2.9%) receiving treatment for less than half the study were excluded.*

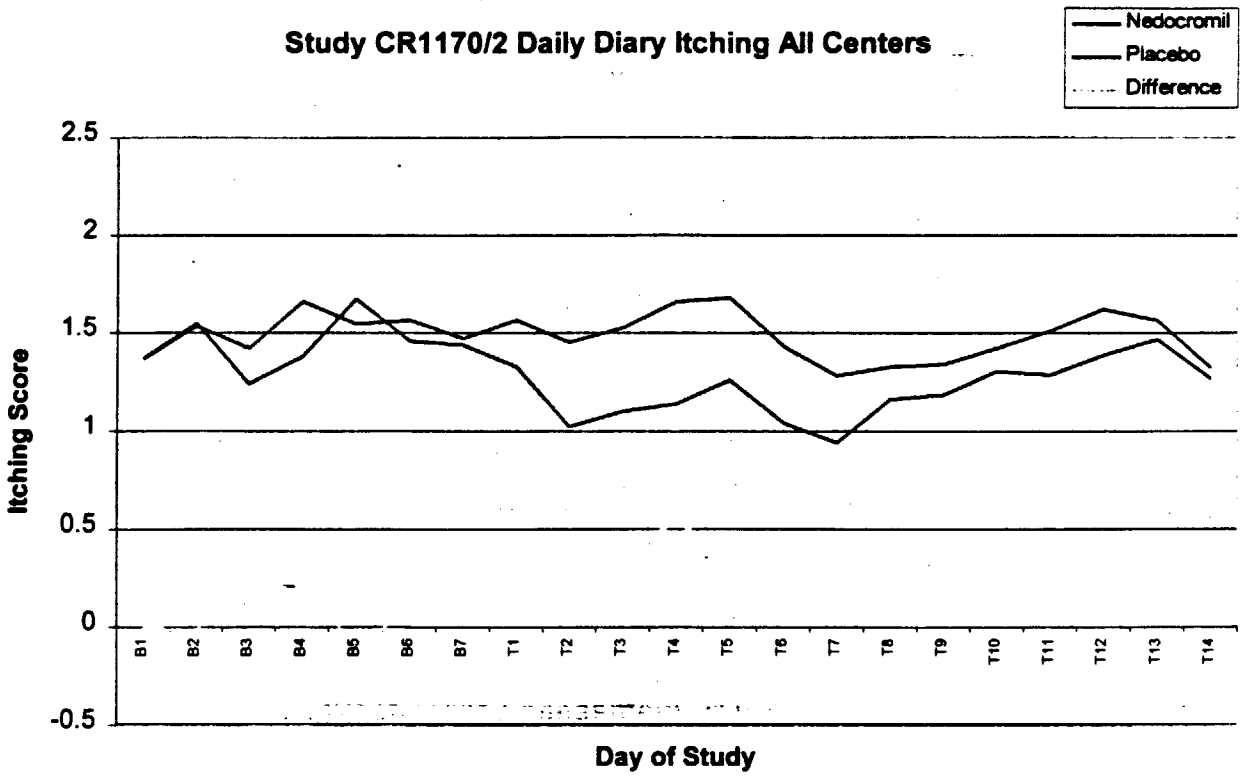
Efficacy:

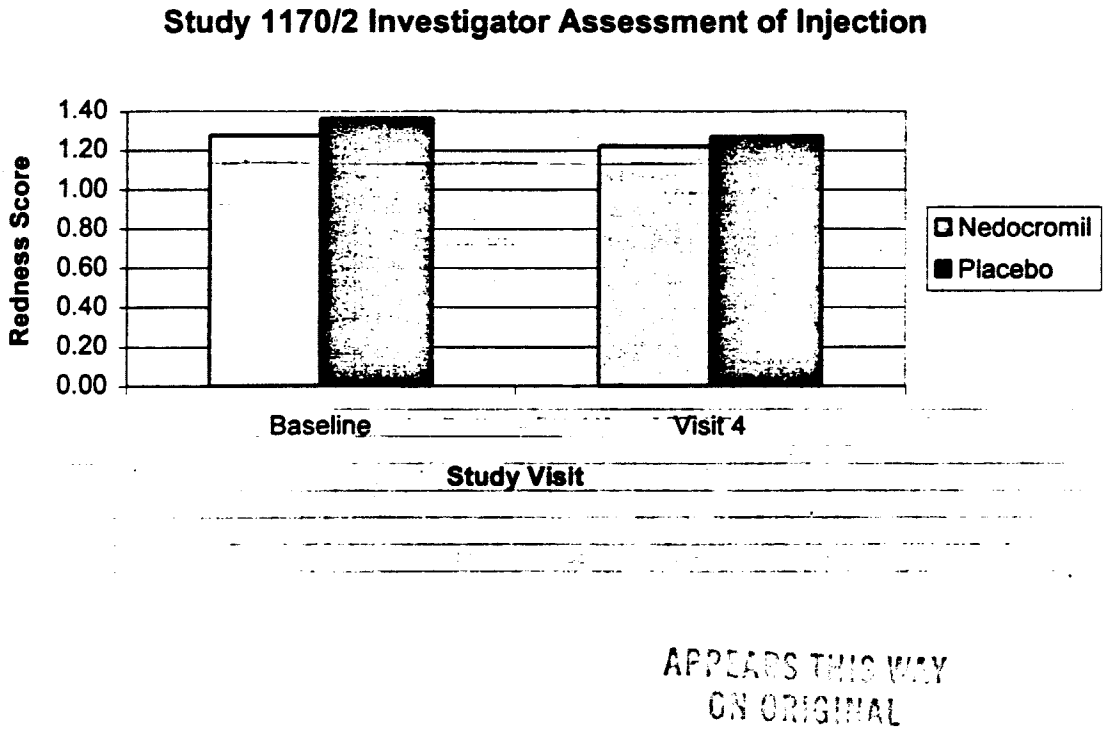


Blumenthal: Minneapolis, MN
Aaronson: Des Plaines, IL
Zeitz: Chicago, IL
Silvers: Englewood, CO

For purposes of analysis, the 14-day period from August 23, 1986 to September 5, 1986 inclusive was designated by the sponsor as the peak pollen period for all four clinics. These days correspond with the first two weeks of treatment with the test medication.

Reviewer Comment: *Acceptable. The pollen counts at each study center justify the sponsor's choice of a peak pollen period.*





Study 1170/2 Statistical Analysis of data

Itching	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's P value	Adjust baseline	Not adjust baseline	Difference
Placebo	1.51	53	1.48	53	-0.03				
Nedocromil	1.44	50	1.19	50	-0.25	0.33	0.176	0.028	0.29
Redness									
Placebo	1.36	53	1.27	52	-0.1				
Nedocromil	1.27	51	1.22	50	-0.06	0.745	0.472	0.327	0.05

Reviewer Comment: *Acceptable. Although the graph shows a trend toward Nedocromil efficacy in reducing itching, this is not statistically significant. The figure and statistics both fail to support the claim of efficacy of Nedocromil in reducing the itching and redness of allergic conjunctivitis.*

Table of Adverse Events:

Preferred Term	Nedocromil	Nedocromil %	Placebo	Placebo %
Headache	6	12%	9	17%
Eye Burning	6	12%	2	4%
Pharyngitis	3	6%	3	6%
Taste perversion	5	10%	0	0%
Coughing	1	2%	4	8%
Nose running	0	0%	4	8%
Bronchospasm	2	4%	1	2%
Eye stinging	1	2%	2	4%
Diarrhea	2	4%	2	4%
Myalgia	2	4%	0	0%
Fever	1	2%	1	2%
Eye grittiness	1	2%	1	2%
Eye dryness	1	2%	1	2%
Post nasal drip	1	2%	1	2%
Eye itching	0	0%	2	4%
Nose blocking	0	0%	2	4%
Vomiting	1	2%	0	0%
Eye redness	1	2%	0	0%
Photophobia	1	2%	0	0%
Corneal ulceration	1	2%	0	0%
Nausea	1	2%	0	0%
Malaise	1	2%	0	0%
Eye soreness	1	2%	0	0%
Migraine	0	0%	1	2%
Nose burning	0	0%	1	2%
Eye irritation	0	0%	1	2%
Dyspepsia	0	0%	1	2%
Rash	0	0%	1	2%
Twitching	0	0%	1	2%
Fatigue	0	0%	1	2%

Reviewer Comment: *Adverse events occurring at ≥5% incidence including headache, burning, pharyngitis, taste perversion, coughing, and nose running will be reported in the label.*

7.1.3 Study #3 Protocol #CR1343/1

Title: A Multicenter Double-masked Group Comparative Study of the Efficacy and Safety of Nedocromil Sodium 2% Ophthalmic Solution in the Treatment of Ragweed Seasonal Allergic Conjunctivitis

Study Objective, Plan, Masking, Concomitant Medication, Flow Chart, Subject Population, Inclusion and Exclusion Criteria, Drug Schedule, and Compliance: Same as CR1170/1.

Reviewer Comment: *Acceptable.*

Study design: Same as study CR1170/1 except for the definition of the efficacy variables.

Study duration: July 15, 1987 to October 17, 1987.

Table of Investigators and Study Centers:

Investigator	Address	City	Country	Number Randomized	Number Completed
James Kreindler, M.D.	7743 Five Mile Road	Cincinnati, OH 45230	USA	37	37
Stephen Rafael, M.D.	15 West Wood Street	Norristown, PA 19401	USA	30	29
Richard Rowe, M.D.	2799 West Grand Blvd.	Detroit, MI 48202	USA	29	29
Robert Schwartz, M.D.	919 Westfall Road Bldg. B	Rochester, NY 14618	USA	25	25
			Total	121	120

Number of subjects (planned and analyzed):

	Sponsor Analysis			Medical Officer Analysis		
	NS02%	Placebo	Total	NS02%	Placebo	Total
Planned			125			125
Pts randomized to treatment	58	63		58	63	
Pts who began treatment	58	63	121	58	63	121
Pts who completed study	57	63	120	57	63	120
Withdrawals	1	0		1	0	1
Treatment failure	0	0		0	0	0
Dropout due to AE	1	0		1	0	1
Other Dropouts	0	0		0	0	0
Analyzed: Efficacy	58	63	121	58	63	121
Analyzed: Safety	48	63	121	48	63	121

Table of Missing Data:

NSO missing data	Reason	Data available	Case Report Form Available	Placebo missing data	Reason	Data available	Case Report Form Available
317	Itching, redness and swelling	baseline & 21d tx	No	None			
329	Never started tx	baseline	No				
332	Never started tx	baseline	No				

Reviewer Comment: *Acceptable.*

Demographics:

Subjects		Nedocromil	% Nedocromil	Placebo	% Placebo
Gender					
	Female	30	52%	38	60%
	Male	28	48%	25	40%
Mean Age (Years)		33.7		32.5	

Reviewer Comment: *Not Acceptable. Patient race and iris color were not provided.*

Criteria for evaluation:

Efficacy:

Diary cards were kept with individual scores recorded for itchy eyes, and "overall eye condition" consisting of all symptoms other than itchy eyes including burning eyes, tearing eyes, redness, swelling and any other symptoms.

The itchy eyes and overall eye condition were assessed daily by the patient on the following five-point scale:

0 = none: symptom absent
1 = mild: symptom barely noticeable
2 = moderate: symptom caused some discomfort
3 = severe: symptom caused much discomfort without interfering with daily routine
4 = very severe: symptom present for most of the day. Caused enough discomfort to interfere with daily routine.

Primary efficacy variable:

"Summary score:" This is defined as the sum of the individual symptom scores for itchy eyes, and overall eye condition enumerated above.

Secondary outcome variables:

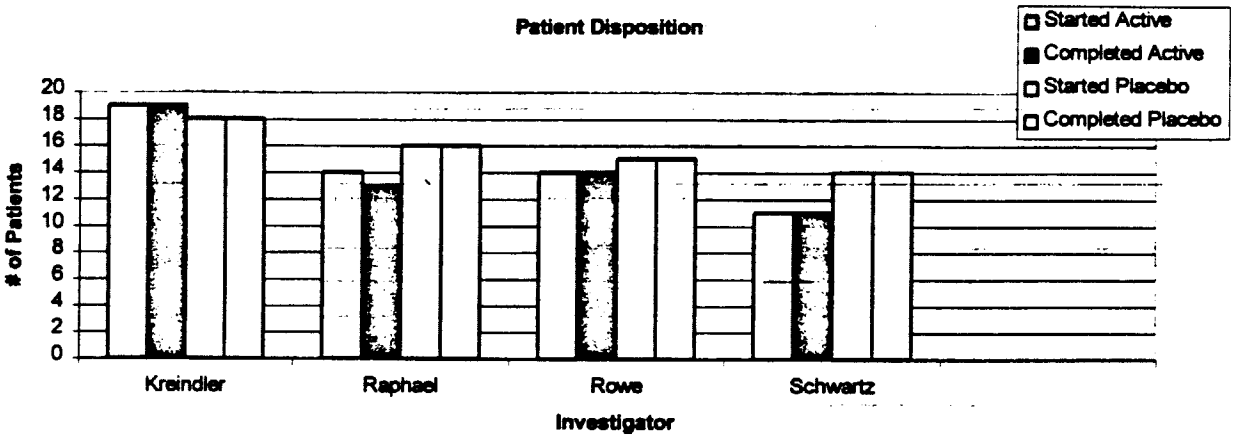
- Clinician assessment at each clinic visit of tearing, conjunctival injection, conjunctival edema and overall severity of conjunctivitis as presented on the day of visit.
- Clinician's and patient's overall opinion of treatment effectiveness.

1 = 100% - fully controlled symptoms
2 = 75% - mostly controlled symptoms
3 = 50% - fairly controlled symptoms
4 = 25% - poorly controlled symptoms
5 = 0% - no control of symptoms

Safety

- Laboratory data: Blood and urine samples were obtained at the initial clinic visit only and were used as a screening criterion.
- Adverse events: At each clinic visit, the investigator questioned the patient regarding any problems. Any adverse events were recorded on the Drug Experience Form.
- External and Slit Lamp Examination: An ophthalmologist performed an external and slit lamp examination at baseline and eight weeks of treatment. The following were assessed:
  - Conjunctival injection and edema
  - Limbal injection and edema

Disposition:



Reviewer Comment: *Acceptable. Each investigator contributes similarly to the number of patients and patient withdrawals. Similar numbers of subjects started and completed the Active and Vehicle groups.*

Withdrawals and Exclusions:

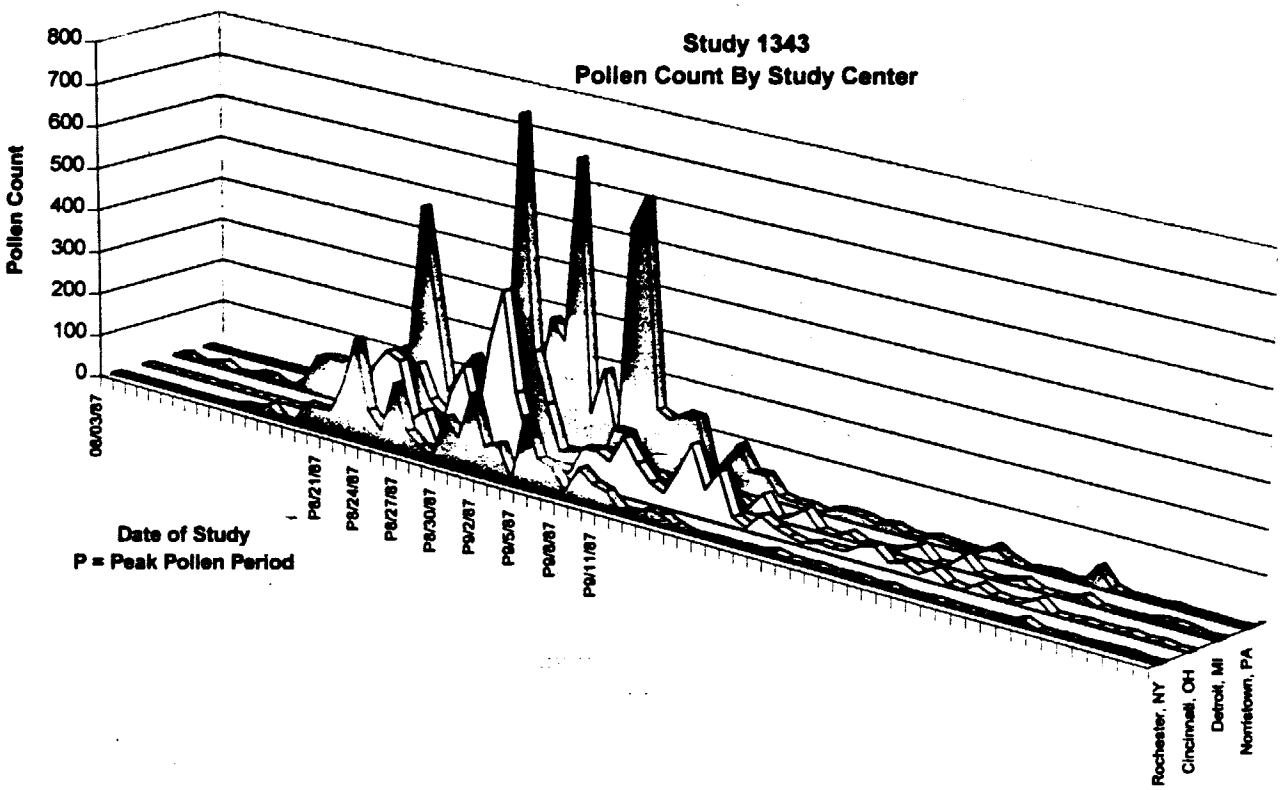
Reasons for patient withdrawal and exclusions were the same as study CR1170/1.

Table of Subject Withdrawals and Exclusions After Randomization

Pt No	Sex	Age	Duration of Treatment	Reason	Treatment	Clinic	Excluded Analysis
04-317	F	32	21 days	Patient developed persistent injection, swelling, and mild itching of conjunctiva of both eyes. Began taking Seldane after 17 days of treatment.	Nedocromil	Raphael	Included

Reviewer Comment: *Acceptable. There were no patient exclusions. Although the above subject withdrew from the study, the data was included for analysis.*

Efficacy:

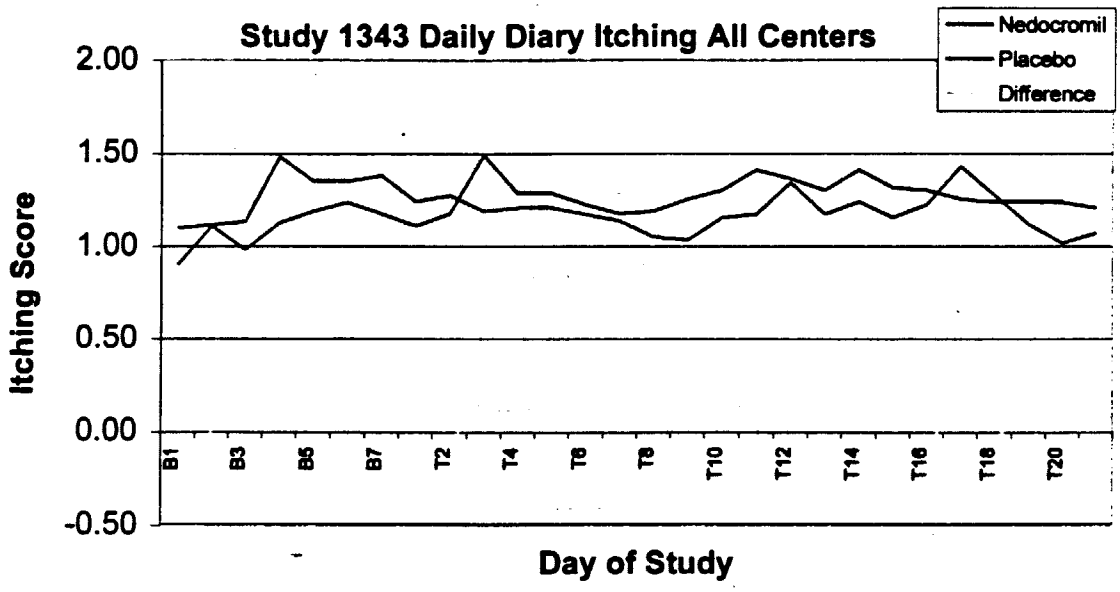


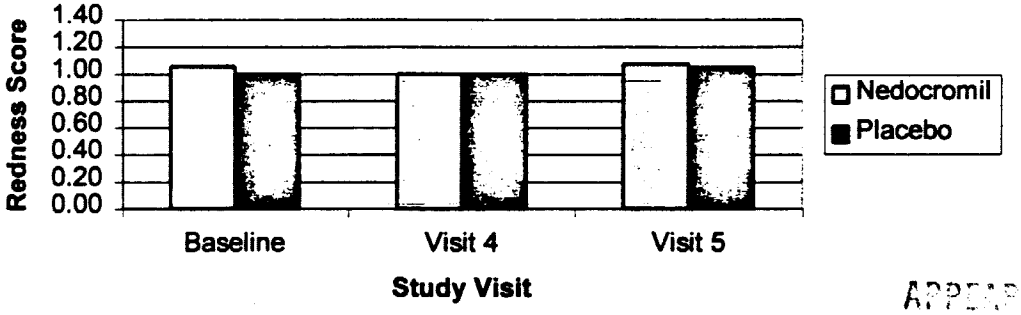
The magnitude of the pollen counts was least in Rochester, NY (Dr. Schwartz), followed by Detroit, MI (Dr. Rowe), Cincinnati, OH (Dr. Kreindler), and Norristown, PA (Dr. Raphael). For purposes of sponsor analysis, the sponsor defined a 21-day peak pollen period in each clinic before unmasking as specified in the table below. The ragweed pollen season began prior to or during the baseline period in each clinic. Once treatment began the first three weeks of double masked treatment represented the continuous time period when the pollen challenge was greatest.

Location	Investigator	Sponsor Peak Pollen Period	Mean Pollen Count	Start Treatment	Minimum # of Days before Peak Pollen Period	# of Subjects	Medical Officer Peak Pollen Period	Medical Officer Baseline Period
Rochester	Schwartz	8/20 to 9/09	85	8/20	0	25	8/20 to 9/9	8/13 to 8/19
Detroit	Rowe	8/21 to 9/10	102.5	8/20	1	29	8/21 to 9/10	8/14 to 8/20
Cincinnati	Kreindler	8/22 to 9/11	116.4	8/20	2	37	8/22 to 9/11	8/15 to 8/21
Norristown	Rafael	8/21 to 9/10	215.9	8/20	1	30	8/21 to 9/10	8/14 to 8/20

Reviewer Comment: *Acceptable. The raw pollen count data are provided. The timing and magnitude of peak pollen counts at each study center justify the sponsor's choice of a peak pollen period.*

Efficacy:





Study 1343 Statistical Analysis

Itching	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's p-value	Adjust baseline	Not adjust baseline	Difference
Placebo	1.1	63	1.27	63	0.17				
Nedocromil	1.3	58	1.18	58	-0.12	0.12	0.027	0.175	0.09
Redness									
Placebo	1	63	1	63	0				
Nedocromil	1.05	58	1	58	-0.05	0.93	0.304	0.556	0

Reviewer Comment:

The sponsor failed to show Nedocromil more efficacious than Vehicle in reducing itching or redness associated with allergic conjunctivitis.

Table of Adverse Events: All centers

Preferred Term	Nedocromil n=58	Percent	Placebo n=63	Percent
Headache	21	36%	22	35%
Pharyngitis	3	5%	4	6%
Arthralgia	2	3%	3	5%
Back Pain	1	2%	4	6%
Eye Burning	3	5%	2	3%
Taste Perversi	3	5%	1	2%
URI	1	2%	3	5%
Fever	1	2%	3	5%
Coughing	1	2%	2	3%
Dysmenorrhea	2	3%	1	2%
Infection, Viral	2	3%	1	2%
Diarrhea	1	2%	1	2%
Conjunctivitis	1	2%	1	2%
Abdominal Pain	1	2%	1	2%
Nausea	1	2%	1	2%
Bronchospasm	1	2%	1	2%
Rhinitis	1	2%	1	2%
Pain	1	2%	1	2%
Nose Blocking	0	0%	2	3%
Arthritis	1	2%	0	0%
Myalgia	1	2%	0	0%
Migraine	1	2%	0	0%
Glaucoma	1	2%	0	0%
Corneal Opacit	1	2%	0	0%
Eye Pain	0	0%	1	2%
Tooth Disorder	1	2%	0	0%
Dyspnea	1	2%	0	0%
Epistaxis	1	2%	0	0%
UTI	0	0%	1	2%
Amenorrhea	0	0%	1	2%
Menstrual Disor	1	2%	0	0%
Chest Pain	1	2%	0	0%
Herpes Simplex	1	2%	0	0%
Tendinitis	1	2%	0	0%
Eye Itching	0	0%	1	2%
Eye Watering	1	2%	0	0%
Eye redness	0	0%	1	2%
Eye Stinging	0	0%	1	2%
Nose Burning	0	0%	1	2%
Nose Running	1	2%	0	0%
Nose Stinging	0	0%	1	2%
Bee sting	1	2%	0	0%

Reviewer Comment: *Acceptable. Adverse events occurring at ≥5% will be reported in the label as appropriate.*

7.1.4 Study #4 Protocol #CR1344

Title: A Multicenter Double-masked Group Comparative Study of the Efficacy and Safety of Nedocromil Sodium 2% Ophthalmic Solution in the Treatment of Ragweed Seasonal Allergic Conjunctivitis

Study Objective, Plan, Masking, Concomitant Medication, Flow Chart, Subject Population, Inclusion and Exclusion Criteria, Drug Schedule, Compliance, and Design: Same as CR1343.

Study duration: July 15, 1987 to October 17, 1987.

Table of Investigators:

Investigator	Address	City, State	Country	# Randomized	# Completed
Malcolm Blumenthal, M.D.	Minneapolis, MN	Minneapolis, MN	USA	29	29
Robert Dockhorn, M.D.	Prairie Village, KS	Prairie Village, KS	USA	28	26
Harold Kaiser, M.D.	Minneapolis, MN	Minneapolis, MN	USA	24	21
Robert Smith, M.D.	Iowa City, IA	Iowa City, IA	USA	30	28
Howard Zeitz, M.D.	Chicago, IL	Chicago, IL	USA	29	28
			Total	140	132

Number of subjects (planned and analyzed):

	Sponsor Analysis			Medical Officer Analysis		
	NSO2%	Placebo	Total	NSO2%	Placebo	Total
Planned			125			125
Pts randomized to treatment	69	71	140	69	71	140
Pts who began treatment	69	71	140	69	71	140
Pts who completed study	63	69	132	63	69	132
Withdrawals	6	2	8	6	2	8
Treatment failure	0	1	1	0	1	1
Dropout due to AE	0	0	0	0	0	0
Other Dropouts	6	1	7	6	1	7
Analyzed: Efficacy	69	71	140	67	71	138
Analyzed: Safety	69	71	140	69	71	140

Demographics:

Subjects		Nedocromil	% Nedocromil	Placebo	% Placebo
Gender					
	Female	34	51%	30	58%
	Male	35	49%	41	42%
Mean Age (Years)		32.4		32.2	

Reviewer Comment: *Not acceptable. Patient race and iris color were not provided.*

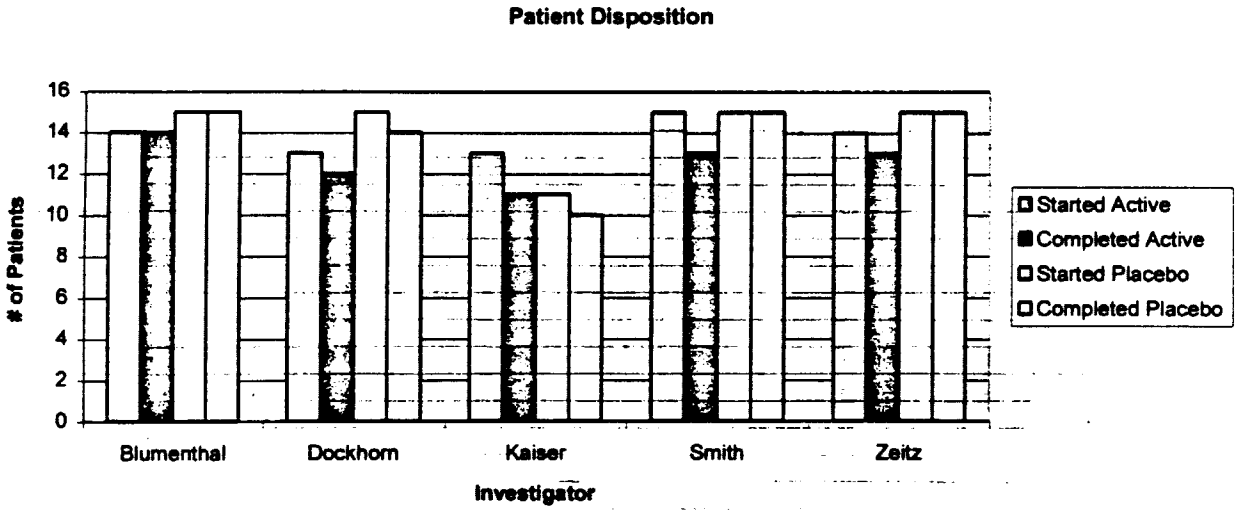
Table accounting for Missing Data:

NSO missing data	Reason	Data available	Case Report Form Available	Placebo missing data	Reason	Data available	Case Report Form Available
130	Never Randomized	None	No	325	Never Randomized	None	No
229	Never Randomized	None	No	326	Never Randomized	None	No
230	Never Randomized	None	No	327	Never Randomized	None	No
329	Never Randomized	None	No	328	Never Randomized	None	No
330	Never Randomized	None	No	224-31	Protocol violation	baseline & 28 d tx	No
530-6	Never Treated	baseline	No	312-8	Tx failure.	baseline & 21 d tx	No
426-10	Lost to follow up	baseline & 8d tx	No				
413-16	Illness-rhinitis	baseline & 10d tx	Yes				
225-32	Illness-sinus infection	baseline & 34 d tx	Yes				
315-19	Illness-URI	baseline & 26 d tx	Yes				
321-21	Illness-ophthalmic burns from disallowed eyedrop	baseline & 13 d tx	Yes				
522-18	Protocol violation-out of area	baseline & 36 d tx	No				
530-6	Never Treated	baseline	No				

Shaded areas indicate subject excluded from medical officer analysis.

Reviewer Comment: *Acceptable. Review of the available case report forms does not show sponsor suppression of data.*

Disposition:



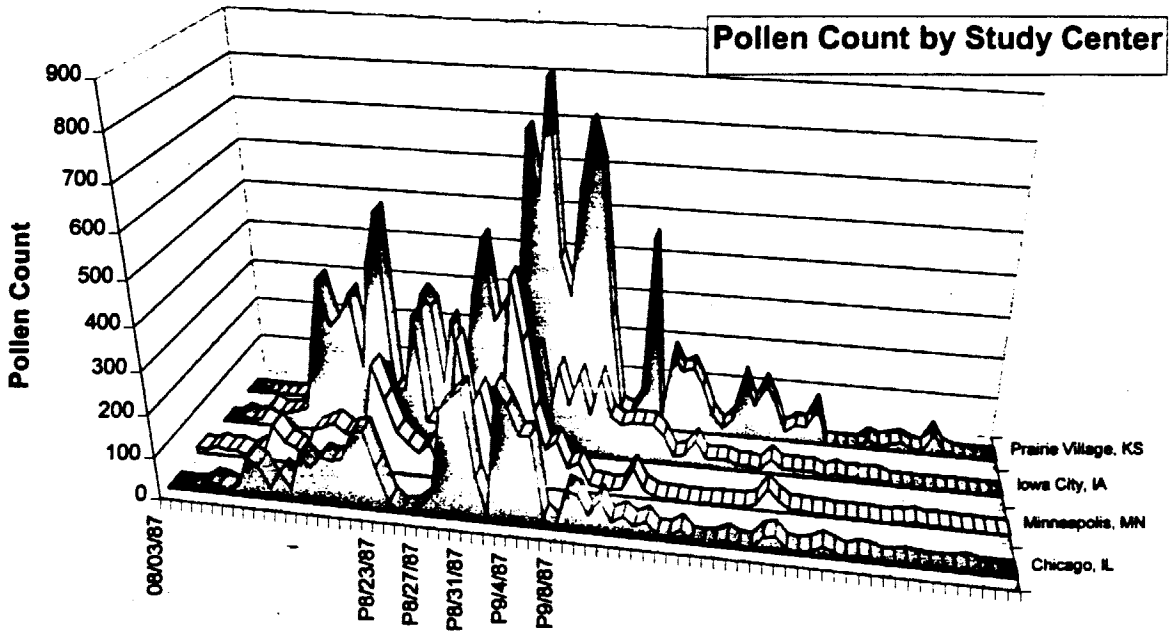
Reviewer Comment: *Acceptable. Each center contributes similarly to the two groups.*

Withdrawals and Exclusions: Reasons for patient withdrawal and exclusions were same as CR1170/1.

Pt No	Sex	Age	Duration of Treatment	Reason	Treatment	Clinic	Excluded Analysis
225-32	F	30	34 days	Intercurrent illness (documented sinus infection)	Nedocromil	Dockhorn	None
315-19	M	27	36 days	Intercurrent illness (documented URI)	Nedocromil	Kaiser	None
321-21	M	12	13 days	Intercurrent illness (Patient used "sting-eze in eye which caused burns)	Nedocromil	Kaiser	None
426-10	F	24	8 days	Lost to follow up.	Nedocromil	Smith	Efficacy
413-16	M	33	10 days	Intolerable rhinitis symptoms	Nedocromil	Smith	Efficacy
522-18	F	33	36 days	Protocol violation and non-compliance. Patient was in Puerto Rico 9/17-9/23 and did not take study medication	Nedocromil	Zeitz	None
224-31	F	37	28 days	Protocol violation. Patient took Benadryl for skin condition	Placebo	Dockhorn	None
312-8	M	49	21 days	Treatment failure. Lack of apparent efficacy.	Placebo	Dockhorn	None

Reviewer Comment: . *Acceptable. Subjects receiving the study drug less than half the peak pollen period (<11 days) were excluded.*

Efficacy:

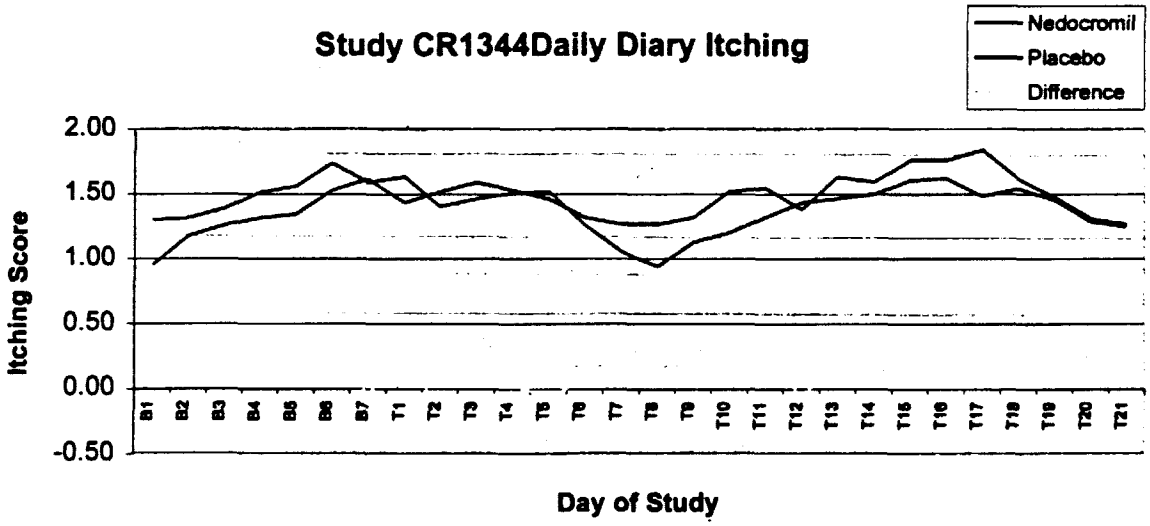


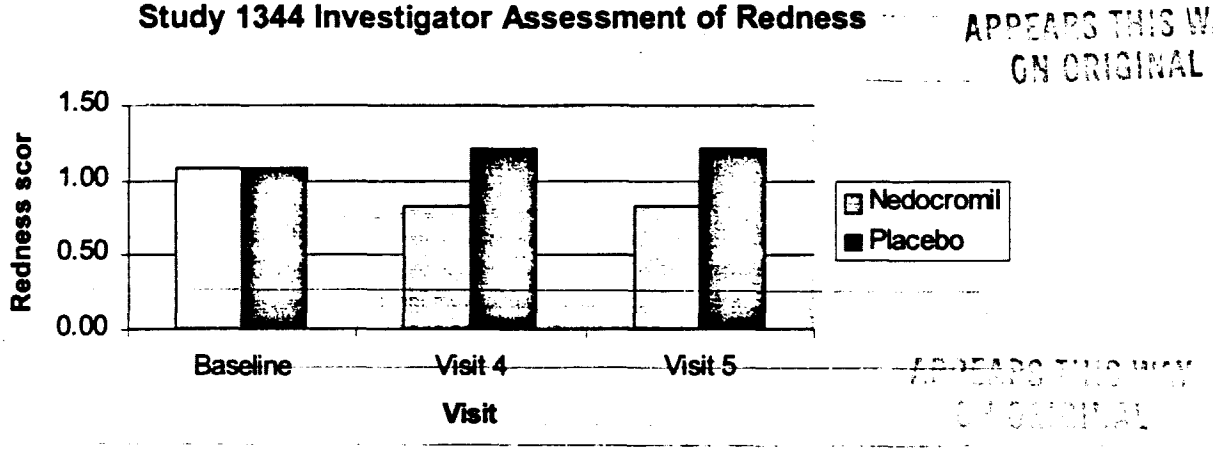
Day of Study
P=Peak Pollen Period

For purposes of analysis, the sponsor defined a 21-day peak pollen period in each clinic before unmasking as the 21-day period from August 21, 1987 to September 10, 1987.

Location	Investigator	Sponsor Peak Pollen Period	Mean Pollen Count	Start Tx	Minimum # of Days before Peak Pollen Period	# of subjects	Medical Officer Peak Pollen Period	Medical Officer Baseline Period
Chicago	Zeitz	8/21 to 9/10	131.1	20-Aug	0	29	8/21 to 9/10	8/14 to 8/20
Minneapolis	Blumenthal/ Kaiser	8/21 to 9/10	148.8	20-Aug	0	53	8/21 to 9/10	8/14 to 8/20
Iowa City	Smith	8/21 to 9/10	200.1	20-Aug	0	30	8/21 to 9/10	8/14 to 8/20
Prairie Village	Dockhorn	8/21 to 9/10	353.5	20-Aug	0	28	8/21 to 9/10	8/14 to 8/20

Reviewer Comment: *Acceptable. The timing and magnitude of peak pollen counts at each study center justify the sponsor's choice of a peak pollen period. The start of treatment is not specified in the report, however the protocol lists August 20, 1987, as the planned start of treatment.*





Study 1344 Statistical Analysis

Itching	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's p-value	Adjust baseline	Not adjust baseline	Difference
Placebo	1.31	71	1.49	71	0.18				
Nedocromil	1.51	67	1.37	67	-0.13	0.09	0.01	0.175	0.12
Redness									
Placebo	1.08	71	1.21	71	0.127				
Nedocromil	1.09	69	0.83	71	-0.26	0.005	0.004	0.002	0.38

Reviewer Comment: *The graph shows a trend toward efficacy in Nedocromil reducing the itching associated with allergic conjunctivitis. This trend is statistically significant if the baseline is adjusted but is not statistically significant if the baseline is not adjusted. The graph and table show Nedocromil to be more efficacious than vehicle in reducing redness associated with allergic conjunctivitis. The table shows this to be statistically significant.*

Adverse Events: All centers

Preferred Term	Nedocromil n=69	Percent	Placebo n=71	Percent
Headache	37	54%	38	54%
Pharyngitis	12	17%	11	15%
URI	10	14%	6	8%
Eye Burning	9	13%	5	7%
Eye Stinging	7	10%	2	3%
Taste perversion	9	13%	0	0%
Infection, viral	3	4%	6	8%
Pharyngitis	4	6%	2	3%
Myalgia	2	3%	2	3%
Eye Itching	1	1%	3	4%
Conjunctivitis	2	3%	1	1%
Dyspepsia	1	1%	2	3%
Vision abnormal	1	1%	2	3%
Pain	1	1%	2	3%
Rash	0	0%	3	4%
Epistaxis	2	3%	0	0%
Dermatitis	1	1%	1	1%
Pruritus	1	1%	1	1%
Arthralgia	1	1%	1	1%
Earache	1	1%	1	1%
Nausea	1	1%	1	1%
Synovitis	1	1%	0	0%
Dizziness	1	1%	0	0%
Application site reaction	1	1%	0	0%
Retinal detachment	1	1%	0	0%
Sinusitis	1	1%	0	0%
Allergies	1	1%	0	0%
Abscess	1	1%	0	0%
Dysmenorrhea	1	1%	0	0%
Urticaria	1	1%	0	0%
Flatulence	1	1%	0	0%
Insomnia	1	1%	0	0%
Micturition frequency	1	1%	0	0%
Nail disorder	1	1%	1	1%
Diarrhea	1	1%	0	0%
Eye irritation	0	0%	1	1%
Eye pain	0	0%	1	1%
Edema	0	0%	1	1%
Anxiety	0	0%	1	1%
Fracture, pathological	0	0%	1	1%
Tooth disorder	0	0%	1	1%
Fatigue	0	0%	1	1%
Face edema	0	0%	1	1%
Photophobia	0	0%	1	1%
Somnolence	0	0%	1	1%
Nose soreness	0	0%	1	1%

Reviewer Comment: *Acceptable. Adverse events occurring at ≥5% incidence, including headache, pharyngitis, upper respiratory tract infection, eye burning, eye stinging, taste perversion, and viral infection will be reported in the label.*

7.1.5 Study #5 Protocol #CR1959

Title: A Multicenter Double-masked Group Comparative Study of the Efficacy and Safety of Nedocromil Sodium 2% Ophthalmic and OPTICROM® 4% Versus Placebo in the Treatment of Ragweed Seasonal Allergic Conjunctivitis

Study Objectives:

Primary Objective

The primary objective of this study was to evaluate the safety and efficacy of nedocromil sodium 2% ophthalmic solution and OPTICROM® 4% solution versus vehicle in the treatment of seasonal allergic conjunctivitis caused by ragweed pollen. Primary efficacy was to be demonstrated by treatment group differences in ocular symptom severity as assessed daily by the patients. The key time frame of evaluation was the two-week period when ragweed pollen counts were highest.

Secondary Objective:

The secondary objective was the comparison of nedocromil sodium with OPTICROM for informational purposes and the comparison of OPTICROM with vehicle as a check on the sensitivity of the trial. The key time frame of evaluation was the two-week period when ragweed counts were the highest.

Study design: Multicenter, randomized, double-masked, group comparative, vehicle-controlled.

Drug Schedule: Study drug was administered as one drop per eye four times daily. The patient received two (2) color labeled bottles, each was used twice daily. The Nedocromil group received 2% nedocromil sodium twice daily plus vehicle twice daily. The vehicle group received vehicle four times daily and the OPTICROM group received OPTICROM four times daily.

Table of Investigators and Study Centers:

Investigator	Address	City, State	Country	Number Randomized	Number Completed
Malcolm Blumenthal, M.D.	Box 434 520 Delaware Street, SE	Minneapolis, MN 55455	USA	30	28
Jordan Fink, M.D.	8799 W. Wisconsin Avenue	Milwaukee, WI 53226	USA	30	30
S. Roger Hirsch, M.D.	5202 W. Oklahoma Avenue	Milwaukee, WI 53226	USA	27	27
Thad Joos, M.D.	20136 Mack Avenue	Gross Pointe Woods, MI 48236	USA	30	30
James Kreindler, M.D.	7743 Five Mile Road	Cincinnati, OH 45230	USA	28	27
Julian Melamed, M.D.	9 Village Square	Chelmsford, MA 01824	USA	30	27
Burton Moss, M.D.	302A East Little Creek Road	Norfolk, VA 23505	USA	28	28
Frank Munden, M.D.	15300 College Blvd.	Lenexa, KS 66219	USA	29	27
Michael Rowe, M.D.	24230 Karim Blvd. Suite 130	Novi, MI 48050	USA	30	30
Howard Zeitz, M.D.	550 W. Webster	Chicago, IL 60614	USA	27	25
				289	279

Study Plan: A multicenter, randomized, double-masked, group comparative, vehicle controlled study. After a one week baseline period, patients were treated with study drug 2% Nedocromil Sodium (NSO), Opticrom 4%, or Vehicle QID for six weeks. A QID regimen was implemented for all three treatments but the nedocromil sodium treated group was only given BID active drug and vehicle on the other two occasions. The baseline period was planned to coincide with the start of the ragweed season. The treatment period was timed to encompass the period of peak ragweed pollen.

Active drug solution: same as study 1170/1

The vehicle solution contained the following:

Riboflavin	0.005%
Benzalkonium chloride (BKC)	0.01%
Edetate disodium (EDTA)	0.05%
Purified water to 100%	

The OPTICROM® solution contained the following:

Cromolyn sodium	4.00%
Benzalkonium chloride (BKC)	0.01%
Edetate disodium (EDTA)	0.10%
Riboflavin	0.0005%
Purified water to	100%

Masking: Same as study CR1170/1

Concomitant Medication:

Permitted:

- Artificial tears.
- Nasal steroid (Beconase AQ®) for rhinitis symptoms.

Not Permitted:

- All other medications

Number of subjects (planned and analyzed):

	Sponsor Analysis				Medical Officer Analysis			
	Nedocromil	Opticrom	Placebo	Total	Nedocromil	Terfenadine	Placebo	Total
Planned	100	100	60	260	100	100	60	260
Randomized	116	115	58	289	116	115	58	289
Began tx	116	115	57	288	116	115	58	289
Completed Study					110	112	57	279
Withdrawal					6	3	1	10
Treatment failure					0	0	0	0
Dropout due to AE					1	0	1	2
Other dropouts					5	3	0	8
*Data returned for analysis								
*Excluded				33				
Analyzed: Efficacy	112	115	57	284	112	115	57	284
Analyzed: Safety	116	115	58	289	116	115	58	289
Withdrawals	5	3	1	9				
Lack of efficacy	0	0	0	0				
Intolerance to study drug	0	1	0	1				
Severe concurrent illness	2	1	0	3				
Non compliance	1	1	0	2				
Adverse Event	1	0	1	2				
Lost to Follow Up	1	0	0	1				

Table Accounting for Missing Data

NSO missing data	Reason	Data available	Days Received Drug	Case Report Form Available	Placebo missing data	Reason	Data available	Days Received Drug	Case Report Form Available
114	Never treated	None	0	No	430	?Never Treated	None	?	No
122	No show to appts	None	6	No	418	Left study area	None	?	No
329	Not Randomized	None		No	529	Not Randomized	None		
330	Not Randomized	None		No	719	Not Randomized	None		
609	Left Study Area	None	?	No	1026	Swollen eye	baseline & 14 d tx	14	Yes
613	Pneumonia	None	4	Yes					
617	Nasal symptoms	Partial	21	Yes					
730	Not Randomized	None							
801	Intolerant to study drug	baseline & 14 d tx	14	Yes					
830	Not Randomized	None							
1006	Moved away from study area	Partial	22	No					
1029	Not Randomized	None							

Gray shading indicates excluded from the medical officer analysis.

Reviewer Comment: *Not acceptable. Subjects receiving opticrom were left out of the electronic database. The case report forms show diary card data available for patient 613 which was left out of the database. This suggests that data may be suppressed by the sponsor. However, this patient meets the sponsor's criteria for exclusion because of the short time the subject received the study drug. The record of treatment received in the case report form for patient 801 was illegible.*

Demographics:

Subjects		Nedocromil	Opticrom	Placebo
Gender				
	Male	47	60	25
	Female	65	55	32
Mean Age (Years)		33.5	33.5	34.2
Age Range (Years)		13-61	14-65	15-62

APPEARS THIS WAY ON ORIGINAL

Reviewer Comment: *Not acceptable. Subject race and iris color were not provided.*

Study Flow Chart

Procedure	Visit 1 Day -1	Visit 2 Day -7	Visit 3 Day 0	Visit 4 Day 7	Visit 5 Day 21	Visit 6 Day 35	Visit 7 Day 56
Randomization	X						
Screening	X						
Start baseline		X					
End baseline			X				
Collection of blood	X						
Collection of urine	X						
Record of AE		X	X	X	X	X	X
External exam				X	X	X	X
Slit Lamp exam				X	X	X	X
Conjunctival injection				X	X	X	X
Conjunctival edema				X	X	X	X
Limbal injection				X	X	X	X
Limbal edema				X	X	X	X
Monitor Diary - Compliance				X	X	X	X

Subject Population: Patients had a history of seasonal allergic conjunctivitis, demonstrated a positive skin test to ragweed antigen, and met the inclusion and exclusion criteria.

Inclusion and Exclusion Criteria: Same as Inclusion and Exclusion Criteria for Study 1170/1

Criteria for evaluation:

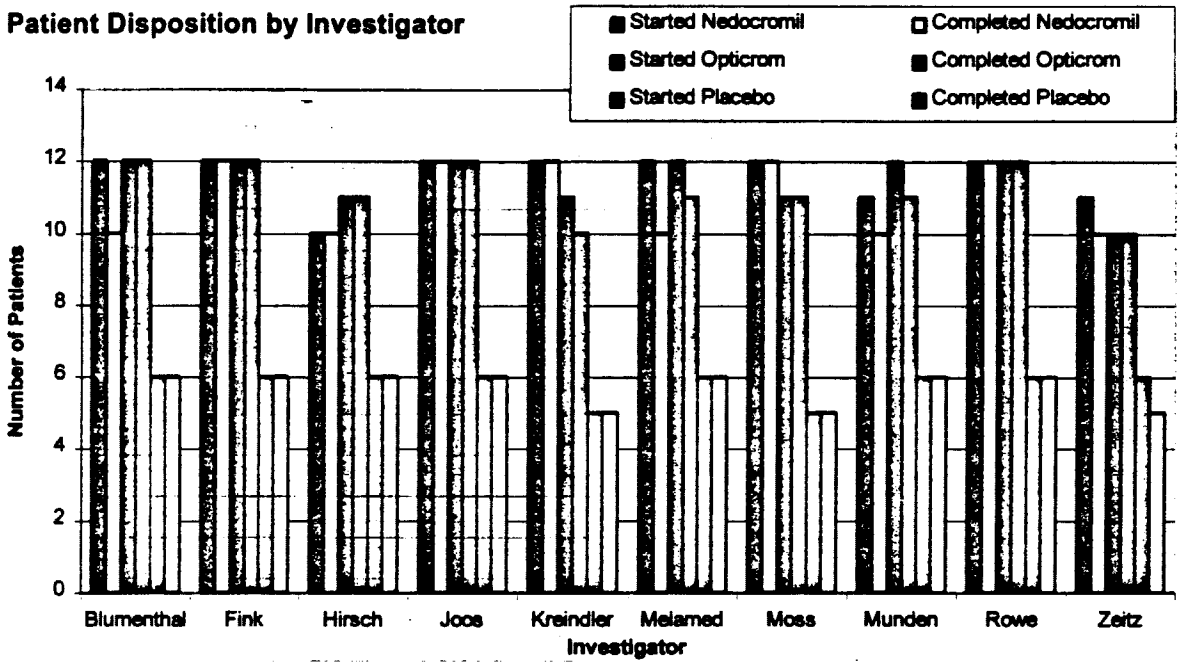
Efficacy:

Primary and Secondary Efficacy Variables: Same as studies 1343 and 1344.

Safety: Same as for studies 1343 and 1344.

Compliance: compliance was assessed by monitoring the patient's daily diary record.

Disposition:



Withdrawals and Exclusions: Patients had the right to withdraw from the study at any time without prejudice and could be withdrawn at the investigator's discretion at any time.

Withdrawals from the study fell into one of the following categories and were to be recorded as such:

- Adverse event or intolerance to nedocromil sodium, OPTICROM 4% vehicle or their constituents or to a required study procedure.
- Failure to return for the follow-up visit and failure to be located by the investigator.
- Intercurrent illness of a nature requiring, in the investigator's judgement, discontinuation of nedocromil sodium, Opticrom 4%, or vehicle treatment or the addition of disallowed medication.
- Non-compliance: failure to maintain diary records, erratic use of study drug, failure to appear for prescribed visits, sue of concomitant medications not prescribed by the investigator, movement outside of the study area.
- An URI during the course of the study.
- Treatment failures such as patients who required the use of ocular or systemic corticosteroids or those who were otherwise determined to be treatment failures at the final patient contact.

Available data from patients who withdrew from the study were included in the analysis as long as they recorded scores for at least half (seven or more) of the days of the peak pollen period. No patients were classified as treatment failures during the course of the study, and no patients required the use of disallowed medication for the control of intolerable conjunctivitis symptoms. There were no withdrawals ascribed to lack of efficacy.

Withdrawals After Randomization: Reasons for patient withdrawal and exclusions were the same as CR1170/1.

Pt No	Sex	Age	Duration of Treatment	Reason	Treatment	Clinic	Sponsor Excluded Analysis
2-114	M	27	0	Patient had to go to Montana and missed two visits during the use of study drug. He was dropped from the study	Nedocromil	Blumenthal	Efficacy
12-122	F	26	6	Patient's job interfered with her participation in the study and she was forced to withdraw. Patient made several appointments but did not show up.	Nedocromil	Blumenthal	Efficacy
19-617	F	40	21	Symptoms were well controlled on study eye medications. Patient was discontinued from the study and placed on systemic corticosteroid for nasal symptoms. Patient completed Visit 5 but did not complete close-out activities.	Nedocromil	Melamed	None
23-613	M	29	4	Patient developed cough, productive brown sputum diagnosed as pneumonia. Theodur and amoxicillin were given to the patient. Patient Visit 4 and close-out activities.	Nedocromil	Melamed	Efficacy
9-801	F	40	14	Patient developed eyeball itching, soreness, swelling and headache since starting study medication. Patient stopped study medication on 8/28/89 and resumed on 8/31/89 after symptoms became better. Symptoms returned 30 minutes after study medication was administered. Patient completed Visit 4 and close-out activities.	Nedocromil	Munden	None
25-1006	F	21	22	Patient moved to Long Island, New York, in job-related relocation. Patient completed Visit 4 and close-out activities	Nedocromil	Zeitz	None
11-525	F	28	28	Patient had sinusitis. Patient completed Visit 4 but did not complete close-out activities	Opticrom	Kreindler	None
4-612	F	45	12	Patient stated that medication made her so miserable and uncomfortable she would rather suffer from her allergies than continue medication. Patient completed Visit 4 and close-out activities.	Opticrom	Melamed	None
13-819	M	44	8	Patient was unable to keep Visit 5 appointment because of business. Patient stopped study medication on 9/03/89. Patient completed Visit 4	Opticrom	Munden	None
23-1026	F	29	14	Patient developed swollen left eye. Patient completed close-out activities and then withdrew.	Placebo	Zeitz	None

Reviewer Comment: *Not acceptable. The sponsor should include patients with partial data available in the database.*

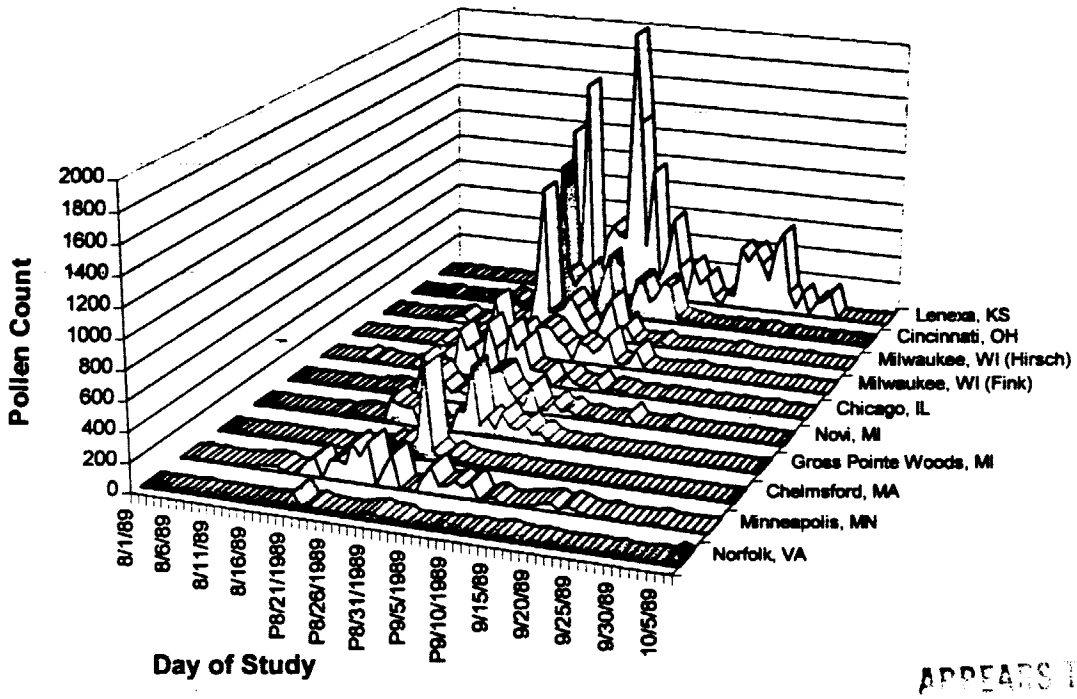
Protocol Deviations:

Pt No	Reason	Treatment	Clinic	Sponsor Excluded Analysis
2-114	Patient had to go to Montana and missed two visits during the use of study drug. He was dropped from the study on 8/29/89. The patient was excluded from all efficacy analyses because the patient's eye symptom severity scores and dosage records were unattainable.	Nedocromil	Blumenthal	Efficacy
12-122	Patient's job interfered with her participation in the study so she was forced to withdraw. Patient made several appointments but did not show up. The patient was excluded from all efficacy analyses because the patient had only six days of treatment.	Nedocromil	Blumenthal	Efficacy
13-418	Patient visited Atlanta, Georgia, from 8/18 to 8/23. This was outside of a ragweed pollen area. These days were excluded from analyses and this patient therefore had insufficient valid data during the baseline period. This patient was excluded from all efficacy analyses.	Placebo	Joos	Efficacy
1-609	Patient visited Orlando, Florida, from 8/25 to 9/1. This was outside of a ragweed pollen area. These days were excluded from analyses and this patient therefore had insufficient valid data during the peak pollen period to be included in the analysis. Since the patient went back to the clinic for Visit 4 (peak pollen visit) after she came back from Florida (09/01), this patient was excluded form all efficacy analyses.	Nedocromil	Melamed	Efficacy
23-613	Patient developed cough, productive brown sputum diagnosed as pneumonia. Theodur and amoxicillin were given to the patient. The patient was excluded from all efficacy analyses because the patient had only four days of treatment.	Nedocromil	Melamed	Efficacy

Reviewer Comment: *The type of analysis from which the protocol deviation patients were excluded by the sponsor is indicated in the table above.*

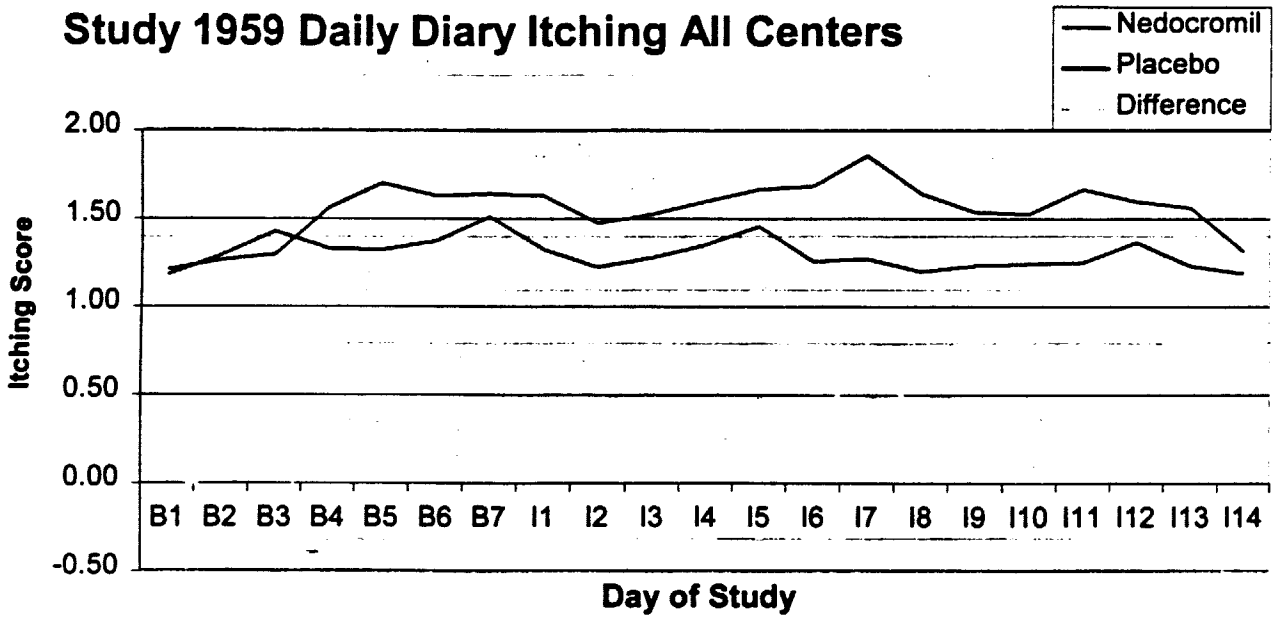
Efficacy: For purposes of analysis, the sponsor defined a peak pollen period in each clinic before unmasking as the 14-day period for each study center outlined in the table. The ragweed pollen season began prior to or during the baseline period in each clinic. Once treatment began the first three weeks of double masked treatment represented the continuous time period when the pollen challenge was greatest.

Study 1959 Pollen Count by Study Center

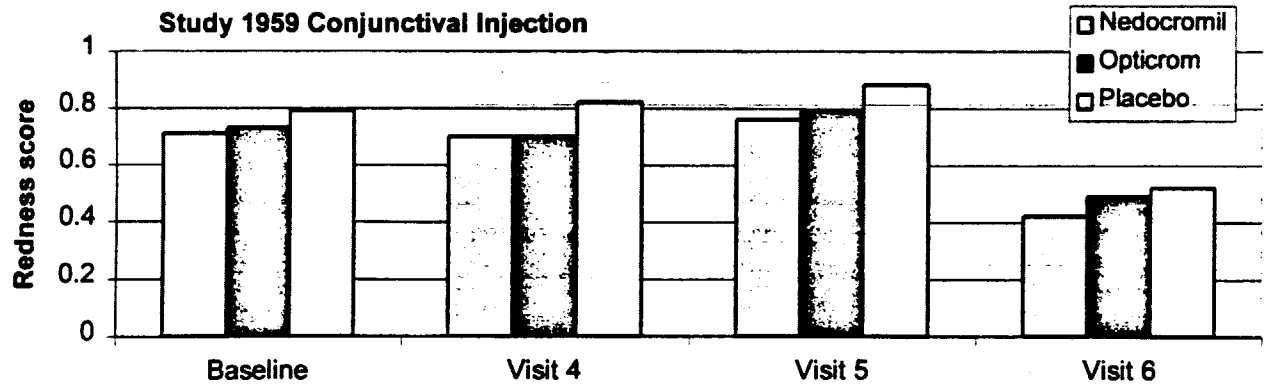


Location	Investigator	Sponsor Peak Pollen Period	Mean Pollen Count	Medical Officer Peak Pollen Period
Minneapolis, MN	Blumenthal	8/23 to 9/5	121	8/23 to 9/5
Milwaukee, WI	Fink	8/25 to 9/7	150	8/25 to 9/7
Milwaukee, WI	Hirsch	8/23 to 9/5	180.5	8/23 to 9/5
Gross Pointe Woods, MI	Joos	8/23 to 9/5	134	8/23 to 9/5
Cincinnati, OH	Kreindler	8/23 to 9/5	281.5	8/23 to 9/5
Chelmsford, MA	Melamed	8/23 to 9/5	57	8/23 to 9/5
Norfolk, VA	Moss	8/23 to 9/5	21	8/23 to 9/5
Lenexa, KS	Munden	8/24 to 9/6	453.5	8/24 to 9/6
Novi, MI	Rowe	8/23 to 9/5	125.9	8/23 to 9/5
Chicago, IL	Zeitz	8/23 to 9/5	164.7	8/23 to 9/5

Reviewer Comment: *Acceptable. The sponsor has justified the peak pollen period.*



Reviewer Comment: *On the graph, the analysis of the data shows marginal efficacy of Nedocromil reducing the itching associated with allergic conjunctivitis.*



Itching	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's p-value	Adjust baseline	Not adjust baseline	Difference	Kruskal-Wallis
Placebo	1.47	57	1.59	57	0.11					
Nedocromil	1.35	112	1.27	112	-0.08	0.072	0.071	0.014	0.32	
Opticrom	1.4	115	1.41	115	0.01	0.262	0.258	0.117	0.18	0.34
Redness										
Placebo	0.46	51	0.82	57	0.36					
Nedocromil	0.41	112	0.7	112	0.29	0.22	0.387	0.194	0.12	
Opticrom	0.36	115	0.7	115	0.34	0.796	0.574	0.225	0.12	0.85

Reviewer Comment: *Nedocromil fails to show efficacy at decreasing investigator assessment of conjunctival injection when compared with Opticrom and vehicle.*

Safety: Adverse Events--All centers

Preferred Term	NSO	OPTICROM	Placebo
Headache	47	37	20
Eye Burning	24	26	6
URI	14	7	5
Eye Stinging	10	14	1
Pharyngitis	6	7	4
Eye Itching	1	5	4
Coughing	5	3	2
Unpleasant Taste	8	0	2
Back Pain	2	6	1
Myalgia	1	4	3
Dysmenorrhea	5	2	0
Pain	1	2	3
Arthralgia	3	2	1
Phinitis	0	3	2
Bronchospasm	2	2	1
Eye Grittiness	2	3	0
Influenza-like Sx	1	1	2
Sinusitis	1	3	0
Fever	1	3	0
Earache	2	2	0
Dyspepsia	2	2	0
Tooth Disorder	0	3	0
Infection, Viral	0	3	0
Conjunctivitis	1	0	2
Allergic Reaction	1	2	0
Sneezing	2	0	1
Cystitis	0	1	1
Blepharospasm	0	1	1
Post Nasal Drip	0	1	1
Abdominal Pain	0	2	0
Epistaxis	0	2	0
Chest Pain	0	2	0
Eye Dryness	0	2	0
Eye Watering	0	2	0
Vision Abnormal	1	0	1
Hypertonia	1	1	0
Nausea	1	1	0
Dyspnea	1	1	0
Rash	2	0	0