

Pruritus	0	0	1
Face Edema	0	0	1
Cramps Legs	0	0	1
Blepharitis	0	0	1
Eye Soreness	0	0	1
Eczema	0	1	0
Urticaria	0	1	0
Migraine	0	1	0
Diarrhea	0	1	0
Gastric Ulcer	0	1	0
Esophagitis	0	1	0
Lymphadenopathy	0	1	0
Eye Irritation	0	1	0
Eye redness	0	1	0
Acne	1	0	0
hypesthesia	1	0	0
Neuralgia	1	0	0
Twitching	1	0	0
Constipation	1	0	0
Gastroenteritis	1	0	0
Fluid Retention	1	0	0
Laryngitis	1	0	0
Pneumonia	1	0	0
Sputum Increased	1	0	0
Renal Calculus	1	0	0
UTI	1	0	0
Otitis Media	1	0	0
Nose Running	1	0	0

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ON ORIGINAL

Reviewer Comment: *Acceptable*

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ON ORIGINAL

## 7.1.6 Study #6 Protocol #CR1871

**Title: A Multicenter Double-Blind Group Comparative Study of 2% Nedocromil Sodium Eye Drops Administered Twice Daily with Placebo Eye Drops in the Treatment of Seasonal Allergic Conjunctivitis in Children**

**Objectives:** To compare the efficacy, of nedocromil sodium with vehicle and to assess its speed of onset of action, safety and tolerability in treating seasonal allergic conjunctivitis in children.

**Duration:** April to June 1989

**Study design:** The trial was designed as a multi-center, double-blind group comparative study with patients entering the study on a predetermined date just before the birch pollen season began. Following a pre-trial visit between one and two weeks prior to the start of the treatment period, patients were randomly allocated to receive either active treatment or vehicle for a period of 4 weeks. Both treatments were to be administered twice daily.

Investigator	Address	City	Country	Number Randomized	Number Completed
Dr Max Kjellman		Linkoping	Sweden	35	33
Dr. Christian Moller		Umea	Sweden	63	63
Dr. L. Sturmberg		Norrkoping	Sweden	26	26
Dr Torsten Berg		Vasteras	Sweden	27	27
			Total	151	149

**Study Plan:** Same as study CR1156

**Concomitant Medication:**

Permitted

- Antastin-Privine QID rescue therapy
- Terfenadine second line therapy
- Topical sodium cromoglycate for rhinitis and asthma
- Topical steroids for rhinitis and asthma

Not Permitted

- Any other eye treatments for allergic conjunctivitis

**Reviewer Comment:** *The permitted medications may confound the efficacy analysis.*

**Demographics:**

Subjects		Nedocromil	Placebo	Percent
Gender	Female	28	29	38%
	Male	49	43	62%
Mean Age (Years)		11.7	12.2	

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

**Number of subjects (planned and analyzed):**

	Sponsor Analysis			Medical Officer Analysis		
	Nedocromil	Placebo	Total	Nedocromil	Placebo	Total
Planned			120			120
Entered	77	74	151	77	74	151
Withdrawn without taking test medication	0	2	2	0	2	2
Analyzed: Efficacy	77	72	149	77	72	149
Analyzed: Safety	77	72	149	77	72	149
Withdrawals				0	2	2
Non compliance				0	2	2
Protocol Violations				3	1	4
Analyzed: Efficacy Per Protocol				74	69	143
Analyzed: Efficacy ITT LOCF				77	72	149

**Table Accounting for Missing Data:**

NSO missing data	Data available	Placebo missing data	Data available
97	None	227	baseline & 5 d tx
99	None		
159	2 d baseline		
183	baseline & 9 d tx		

**Study Flow Chart**

	Baseline	Treatment (Nedocromil or Placebo)				Final
		1	2	3	4	
Weeks	-1					
Visits	1	2				3
Lab	1					2

ACCEPTED THIS WAY  
ON ORIGINAL**Subject Population**

Patients had a history of seasonal allergic conjunctivitis, and met the inclusion and exclusion criteria.

**Inclusion Criteria**

- Males or females, aged 6-16 years, who were able to comply with test procedures.
- Patients diagnosed as suffering from seasonal allergic conjunctivitis due to birch pollen and exhibited eye symptoms and signs such as itching, soreness, photophobia, redness, grittiness and watery discharge.
- Patients with concomitant rhinitis or asthma were to be included
- Patients who were able to remain within their environment for the duration for the duration of the study.
- Patients who had a positive skin reaction and/or RAST test to birch pollen

**Exclusion Criteria**

- Patients with any additional eye disorder which might have interfered with the study.
- Patients using systemic or ophthalmic topical corticosteroids, antihistamines or ophthalmic sodium cromoglycate, from one week before Visit 2 and throughout the treatment period.
- Patients who wore or intended to wear contact lenses during the treatment period.
- Patients who had commenced hyposensitisation treatment during the previous twelve months.
- Patients known to be sensitive to nedocromil sodium, BKC, EDTA or riboflavin vehicle colorant.
- Patients who were pregnant or at risk of pregnancy during the treatment period.
- Patients who were lactating during the treatment period.

**Reviewer Comment:**            *Acceptable.*

**Criteria for evaluation:**

**Efficacy:**

**Assessment by the Investigator**

Current eye symptoms were assessed at each visit on the following scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Very Severe

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OK ORIGINAL

After 4 weeks' treatment the investigators opinion of treatment efficacy was recorded on the following scale:

- 0 = No control of symptoms
- 1 = Slight control of symptoms
- 3 = Full control of symptoms

**Assessment by the patient:** Throughout the four week period of treatment, the patient/parent recorded the severity of each eye symptom on a 0 – 4 scale similar to that listed above. The number of times per day the rescue medication was used was recorded. At visit 3 the patient gave his/her opinion of the test treatment on a 0 – 3 scale similar to the investigator's opinion of treatment efficacy recorded above.

**Primary Variables**

- Diary card assessments
- Patients opinion
- Clinician's opinion
- Acceptability

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**Secondary Variables**

- Speed of onset of action
- Clinician's opinion of treatment
- Clinical assessment of patient's symptoms
- Use of rescue medication
- Redness and photophobia

**Safety:**

At visits 2 and 3 or at the time of withdrawal, the clinician inquired about, assessed and recorded any adverse effects.

Blood and urine samples were taken at visits 1 and 3 for examination as follows:

Blood: Hemoglobin, MCH, MCHC, PCV or hematocrit, red cell count, white cell count (and differential if total count was abnormal), platelets, sodium, potassium, creatinine, SGOT, SGPT. The protocol state that if necessary micromethods may be used.

Urine: Blood, sugar, protein. A dipstick method was considered to be adequate for these measurements.

**Reviewer Comment:** *Acceptable.*

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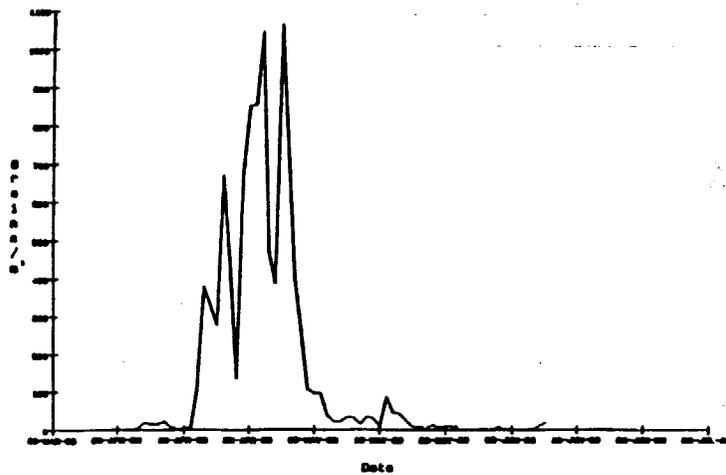
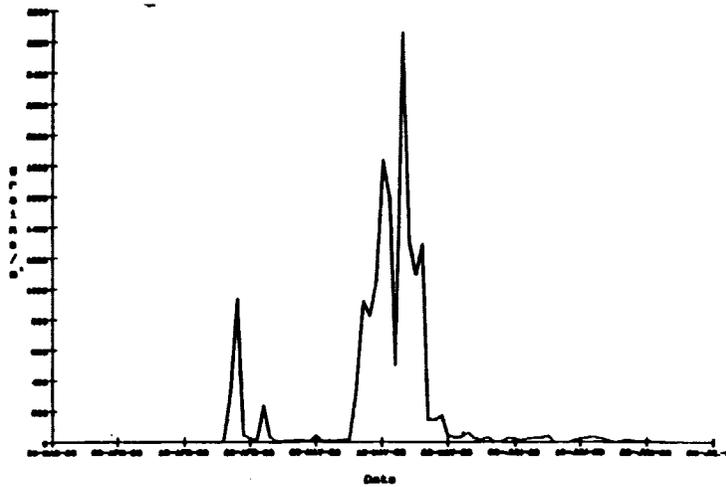
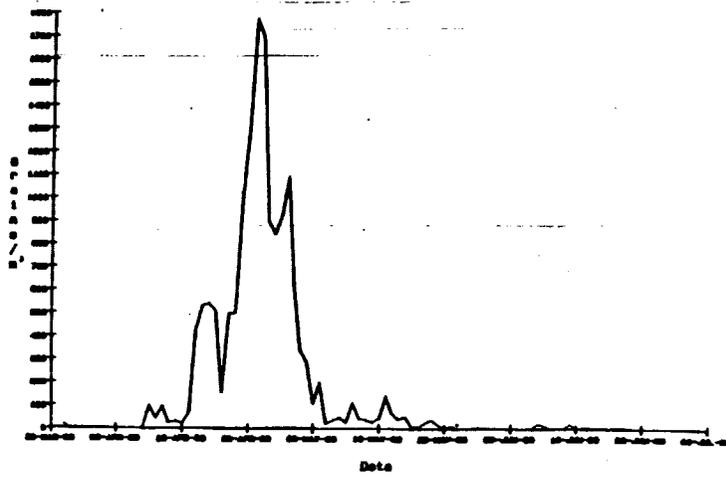
**Withdrawals and Exclusions:** Patients were allowed to withdraw from the study for any reason.

**Table of Withdrawals, Exclusions, and Protocol Deviations:**

Pt No	Days of Tx	Reason	Treatment	Clinic	Sponsor Excluded Analysis	Medical Officer Per Protocol Cases Observed	Medical Officer ITT LOCF
97	0	Excluded-Never took tx	Placebo			Excluded	Excluded-no data
99	0	Excluded-Never took tx	Placebo			Excluded	Excluded-no data
82	27d	Took antihistamine throughout the trial	Nedocromil	Linkoping	Efficacy Safety	Excluded	Included
166	20d	Took 8 corticosteroid tablets on 1 day during fourth week of trial	Nedocromil	Umea	Symptoms scores from time of taking corticosteroid. All rescue treatment.	Excluded	Included
183	19d	Took a corticosteroid during the third week of treatment	Nedocromil	Umea	Symptoms scores from time of taking corticosteroid. All rescue treatment.	Excluded	Included
224	32d	Test treatment not taken on 2 days during first week of treatment	Placebo	Nonkoping	Symptom scores for 2 days	Excluded	Included
227	12d	Test treatment taken for 5 days, stopped for 9 days (no scores recorded), taken for 1 day then stopped until the end of the study	Placebo	Nonkoping	Symptom scores for last 2 days of peak pollen period.	Excluded	Included Partial data
240	20d	No symptoms, did not know how to use the test treatment	Placebo	Nonkoping	Efficacy Safety	Excluded	Included

**Reviewer Comment:** *The sponsor has not submitted some raw data on days the patients above took prohibited medication. The reviewer cannot verify that the sponsor has not suppressed data. For the purposes of this review, all patient raw data available were included for an intent-to-treat last-observation-carried forward analysis as well as a per-protocol analysis.*

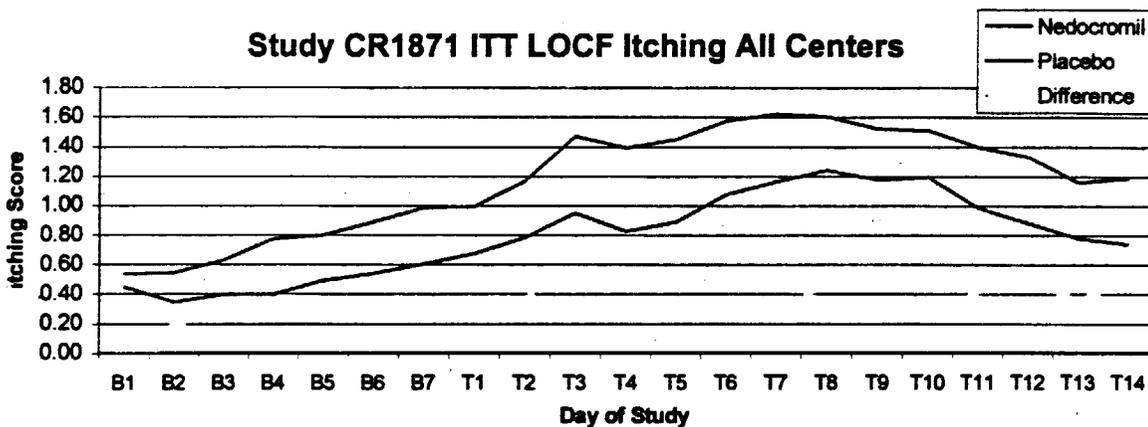
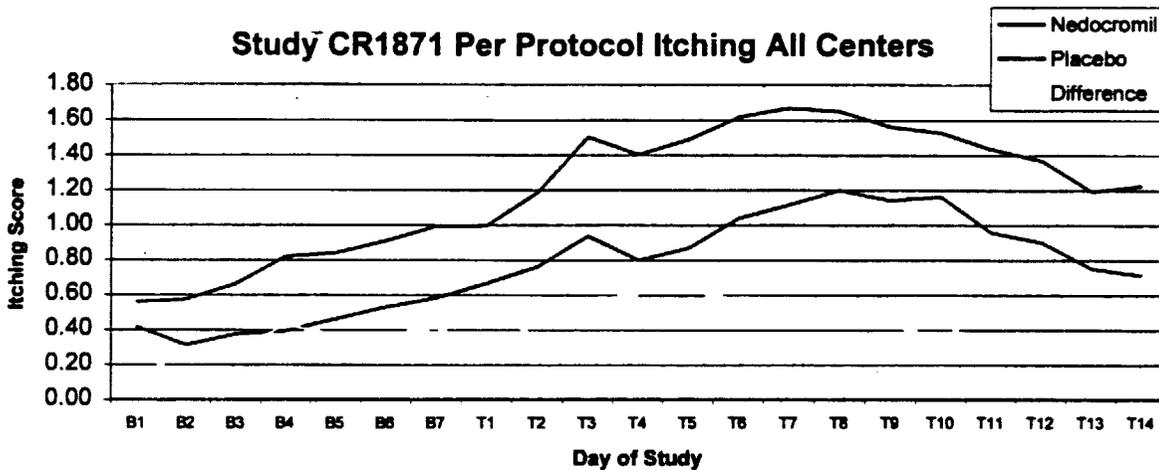
Efficacy:

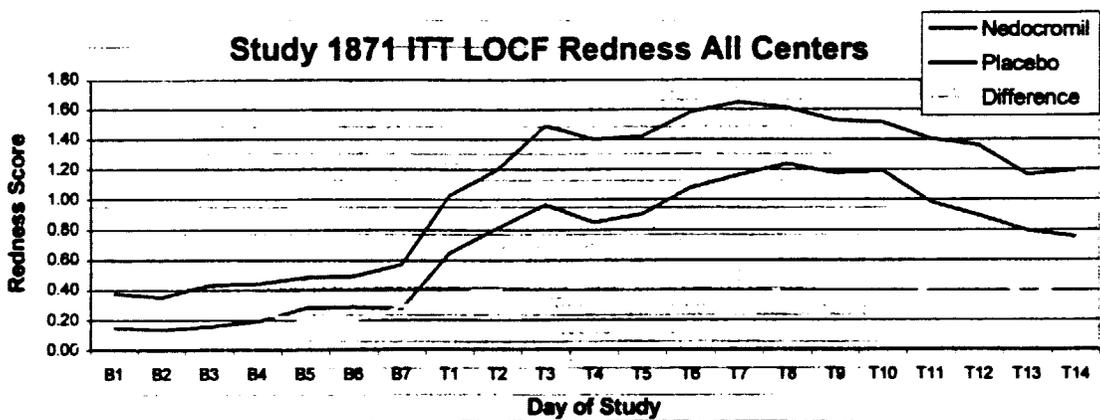
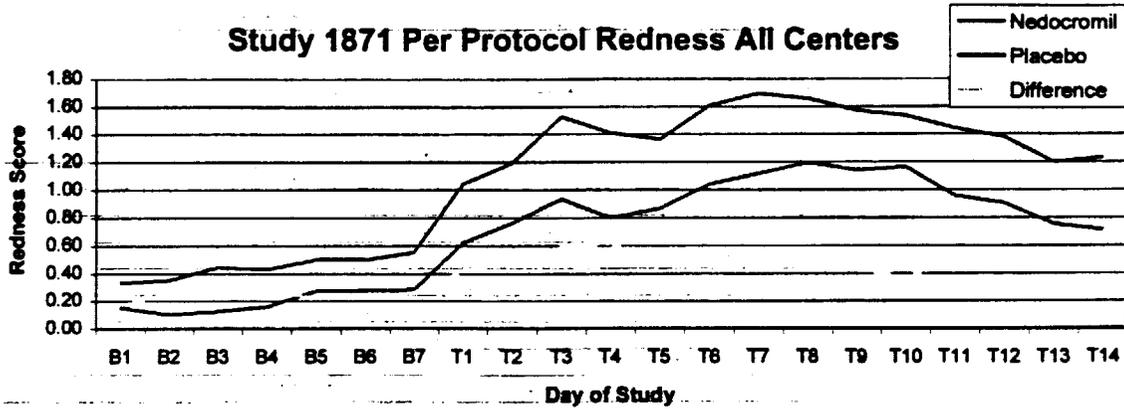


Location	Sponsor Peak Pollen Period 1	Mean Pollen Count	Start Treatment	Minimum # of Days before Peak Pollen season	# of Patients	Medical Officer Peak Pollen Period	Medical Officer Baseline Period
Vasteras	4/24 to 5/10	751.6 grains/m <sup>3</sup>	4/24 to 4/25	0	16	4/24 to 5/5	4/17 to /23
Norrkoping/ Linkoping	4/24 to 5/10	505.9 grains/m <sup>3</sup>	4/24 to 4/25	0	33	4/24 to 5/5	4/17 to 4/23
Umea	4/15 to 5/28	995.4 grains/m <sup>3</sup>	5/10 to 5/11	4	39	5/15 to 5/28	5/8 to 5/14

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**Reviewer Comment:** *Acceptable. Although the raw pollen count data are not provided, the graphic representation of the peak pollen period is clearly legible. The sponsor has justified the choice of the peak pollen period. For the purposes of this review, a seven-day baseline and fourteen-day treatment period were defined for each center based on the start of the peak pollen season.*





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**Statistical Analysis Study 1871**

Itching Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust Baseline	Difference
Placebo	0.78	62	1.42	70	0.68	Not done	0.019	0.0008	0.49
Nedocromil	0.5	70	0.93	73	0.45				
ITT									
Placebo	0.77	64	1.44	72	0.69	Not done	0.04	0.005	0.43
Nedocromil	0.52	73	1.01	76	0.51				

Redness Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust Baseline	Difference
Placebo	0.46	63	1.43	70	0.97	Not done	0.019	0.0005	0.5
Nedocromil	0.25	69	0.93	73	0.68				
Redness ITT									
Placebo	0.47	65	1.44	72	0.98	Not done	0.037	0.003	0.44
Nedocromil	0.25	72	1	77	0.74				

**Reviewer Comment:** Both the graphic and statistical analysis show efficacy for Nedocromil reducing the itching and redness associated with allergic conjunctivitis.

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**Adverse Events:**

Table of "Unusual Symptoms" reported during the study:

Pt #	Symptom	Severity	Duration & Frequency	Treatment
11	Peculiar Taste	Mild	-	Nedocromil
13	Pain on using drops	Mild	20 days	Nedocromil
14	Rhinitis	Severe	12 days	Nedocromil
21	Itching	Mild	29 days	Nedocromil
24	Coughing	Mild	6 days	Nedocromil
25	Watering nose	Mild/Moderate	20 days	Nedocromil
26	Coughing	Moderate	10 days	Nedocromil
79	nasal problem	Moderate	23 days	Nedocromil
81	Asthma	Mild	5 times	Nedocromil
92	Asthma	Mild/Moderate	on 3 days	Nedocromil
92	Sore Eyes	Moderate	1st week	Nedocromil
93	Cold	Moderate	8 days	Nedocromil
94	Nasal Allergy	Moderate	6 days	Nedocromil
100	Asthma	Mild/Moderate	Rather often	Nedocromil
105	Pharyngitis	Moderate	4 days	Nedocromil
146	Itching	Mild	2 minutes	Nedocromil
152	Smarting pain	Mild	0.5 minutes	Nedocromil
156	Smarting pain	Moderate	0.3 minutes	Nedocromil
160	Smarting pain	Mild	0.1 minute	Nedocromil
163	Smarting pain	Mild	0.05 minutes	Nedocromil
171	Smarting pain	Mild	0.25 minutes	Nedocromil
173	Smarting pain	Mild	0.2 minutes	Nedocromil
190	Smarting pain	Mild	2 minutes	Nedocromil
199	Smarting pain	Mild	0.1 minute	Nedocromil
201	Smarting pain	Mild	3 minutes	Nedocromil
206	Smarting pain	Mild	0.2 minutes	Nedocromil
206	Itching	Mild	1 hour	Nedocromil
206	Bad taste	-	5 minutes	Nedocromil
207	Itching	Mild	0.2 minutes	Nedocromil
12	Itching	Moderate	24 days	Placebo
15	Eczema	Very severe	Not stated	Placebo
16	Asthma	Moderate	4 days	Placebo
22	Itching	Mild	4 days	Placebo
75	Asthma	Severe	3 days	Placebo
77	Asthma	Mild	Now and then	Placebo
80	Asthma	Mild	once	Placebo
85	Soreness/eye	Severe	22 days	Placebo
88	Itching	Moderate	2 days	Placebo
91	Asthma	Mild/Moderate	Now and then	Placebo
107	Urticaria	Severe	Not stated	Placebo
107	edema	Severe/Very Se	Not stated	Placebo
107	Asthma	Moderate	Occasionally	Placebo
150	Smarting pain	Mild	0.2 minutes	Placebo
167	Smarting pain	Mild	0.05 minutes	Placebo
174	Smarting pain	Mild	2 minutes	Placebo
195	Smarting pain	Mild	0.25 minutes	Placebo
200	Smarting pain	Moderate	2 minutes	Placebo

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ORIGINALReviewer Comment: *Acceptable.*APPEAR ON THE WAY  
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## 7.1.7 Study #7 Protocol #CR1156

**Title: A Multicenter Double-Blind Group Comparative Study of Nedocromil Sodium 2% Eye Drops in the Treatment of Ragweed Seasonal Allergic Conjunctivitis**

**Objectives:** To compare the efficacy, safety and acceptability of nedocromil sodium eye drops given topically twice daily to that of a vehicle eye drop given twice daily in the treatment of seasonal allergic conjunctivitis.

**Duration:** August 1986 to October 1986

**Study design:** This study was designed as a randomized, double-blind, group comparative multi-center study with patients receiving either nedocromil sodium eye drops or vehicle eye drops.

**Table of Investigators:**

Investigator	Discipline	City	Country	# Randomized	# Completed
J. Greenbaum	Allergist	Hamilton, Ontario	Canada	48	44
A. Vayalumkal	Ophthalmologist	Hamilton, Ontario	Canada		
C. Marshall	Allergist	St Catherine's, Ontario	Canada	36	31
G. Scaife	Ophthalmologist	St Catherine's, Ontario	Canada		
M. Alexander	Allergist	Niagra Falls, Ontario	Canada	37	28
R.D. Merritt	Ophthalmologist	Niagra Falls, Ontario	Canada		
			Total	121	103

**Reviewer Comment:** *Not acceptable. The sponsor should give information on the numbers of patients initially randomized to each center. The sponsor states that 48 patients completed in Hamilton Ontario, data for only 44 subjects was provided. Although the sponsor states that 36 subjects completed in St. Catherine's, data for only 31 was provided. Although the sponsor states that 37 subjects completed in Niagra Falls, data for only 28 was provided. Although most of the deleted data is accounted for in the tables of withdrawals, it is not clear whether or not many of these subjects received treatment. The sponsor should provide data for all randomized subjects, even if they were withdrawn prior to receiving treatment. It is not clear that the sponsor did not suppress data in this study.*

**Study Plan:** One drop was given to each eye, twice daily. The drop size was approximately 0.04 ml which is equivalent to 0.8 mg of nedocromil sodium. Total daily dose was 3.2 mg. The active drug solution contained the following:

Nedocromil sodium	2.00%
Benzalkonium chloride (BKC)	0.01%
Edetate disodium (EDTA)	0.05%
NaCl	0.55%
Purified water to 100%	

A vehicle eye drop was given containing the same concentration of BKC and EDTA in aqueous isotonic solution with a yellow coloring.

**Reviewer Comment:** *Acceptable.*

**Concomitant Medication:****Permitted**

- Naphazoline hydrochloride (Vascon)
- Topical nasal medication for allergic rhinitis.
- Three-day course of prednisone, maximum dose 20 mg/day.

**Not Permitted**

- Sodium cromoglycate eye drops.
- Systemic antihistamines or medications with antihistamine effects.
- Systemic or topical steroids.

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ON ORIGINAL

**Reviewer Comment:** *The permitted medications may confound the efficacy analysis.*

**Number of subjects (planned and analyzed):**

	Sponsor Analysis			Medical Officer Analysis		
	Nedocromil	Placebo	Total	Nedocromil	Placebo	Total
Planned			120			
Entered	60	61	121	60	61	121
Left out of database by Sponsor (not clear if received study drug)	11	7	18	11	7	121
Included in Database				49	54	103
Analyzed: Efficacy	49	53	102			
Analyzed: Safety			103			
Exclusions: Withdrawals				0	3	3
Exclusions: Protocol Violations				11	17	28
Treatment failure				0	0	0
Dropout due to AE				0	0	0
Analyzed: Efficacy Per Protocol				39	35	74
Analyzed: Efficacy ITT LOCF				49	53	102

**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
3	Presumed Never treated	None	No	5	Presumed Never treated	None	No
43	Non cooperation	baseline & 7d tx		32	Presumed Never treated	None	No
44	Presumed Never treated	None	No	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	Presumed Never treated	None	No	94	Presumed Never treated	None	No
74	Presumed Never treated	None	No	71	Disallowed medication	Baseline & 9 d tx	No
97	Presumed Never treated	None	No	78	?	Baseline & 6 d tx	No
101	?	Baseline & 5 d tx	No	105	?	Baseline & 5 d tx	No

**Demographics:**

Subjects		Nedocromil	Placebo	Percent
Gender	Female	32	32	62%
	Male	17	22	38%
Mean Age (Years)		25.4	25.1	

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

**Study Flow Chart**

	Baseline	Treatment (Nedocromil or Placebo)				Final
Weeks		1	2	3	4	
Visits	1	2	3	4		5

**Subject Population:** Patients had a history of seasonal allergic conjunctivitis, and met the inclusion and exclusion criteria.

**Inclusion Criteria**

- Males or females, aged 10 years or over, who were able to comply with test procedures.
- Patients with a positive skin test to ragweed and a history of being symptomatic to no other allergens that affected the eye between 1 August to 30 September.
- Patients who have been treated for allergic conjunctivitis to ragweed for at least two previous occasions
- Patients with concomitant rhinitis or asthma were to be included
- Patients had to remain in the Southwestern Ontario area for the duration of the study.
- Patients had to give written informed consent to the study.

**Exclusion Criteria**

- Patients with any additional eye disease which might have interfered with the study.
- Patients with significant renal, hepatic, cardiovascular or hematopoietic diseases.
- Patients who suffered from a condition that, in the opinion of the investigator, would make the participation in the study hazardous or liable to obscure the evaluation of drug effect.
- Patients who would have worn contact lenses during the course of the study.
- Patients who were undergoing routine immunotherapy or Pollinex R shots for the first time.
- Patients who had received Pollinex R shots since the last season.
- Patients who needed to take systemic steroids for more than three days at a maximum daily dose of 20 mg.
- Patients who needed to take systemic antihistamines or topical sodium cromoglycate.
- Patients who were pregnant or who were likely to become pregnant during the study.
- Patients who were lactating.

**Reviewer Comment:** *Acceptable.*

**Criteria for evaluation:****Efficacy:****Global Opinions****Patient's opinions**

At the end of the trial the patients were asked to rate the effectiveness of the treatment using the scale detailed below:

- 0 = No control
- 1 = Slight control
- 2 = Moderate control of symptoms
- 3 = Full control of symptoms

**Investigator's opinion**

At the end of the trial the investigator was asked to rate the effectiveness of the treatment using the 0 – 3 scale as detailed above.

**Diary Card Assessments**

Each day during the trial the patients were to record the severity of the following diary card variables using a 0 – 4 scale detailed below:

Diary card variables:

- Itching eyes
- Soreness of eyes
- Grittiness of eyes
- Watering of eyes
- Redness of eyes
- Light hurting eyes
- Eye condition in general

- 0 = No symptoms
- 1 = Mild symptoms (just noticeable)
- 2 = Moderate symptoms (noticeable but tolerable)
- 3 = Severe symptoms (severe enough to interfere with daily activities)
- 4 = Very severe symptoms (intolerable – all daily activities disrupted)

**Primary Variables**

- Diary card assessments
- Patients opinion
- Clinician's opinion
- Acceptability

**Safety:**

**Ophthalmic Examination**

At each visit an ophthalmologist assessed for any changes noted by a slit-lamp examination and the measurement of intraocular pressure

**Laboratory Data**

At each visit a blood sample was taken for:

- Immunology: Total serum IgE
- Hematology: FBC, differential blood count
- Biochemistry: Electrolytes; total protein, albumin, bilirubin, creatinine, alkaline phosphatase, SGOT, SGPT, BUN, uric acid, glucose, Ca<sup>++</sup>, P<sub>04</sub>.

**Recording of Suspected Adverse Reactions**

At each visit the investigator discussed with the patient any complaints which might have been adverse drug reactions. Any complaint which the investigator regarded as "possible" or "probable" reactions to the trial treatment were to be entered on the assessment form.

**Reviewer Comment:** *Investigator interpretation of adverse events prior to entry on assessment form may result in under-reporting of adverse events.*

Table of Protocol Deviations

Pt No	Reason	Treatment	Per Protocol Observed Cases	ITT LOCF
8	Tavist	Nedocromil	Exclude	Include
11	Seldane	Nedocromil	Exclude	Include
31	No baseline, Chlor-Tripolon	Nedocromil	Exclude	Include
36	Chlor-Tripolon	Nedocromil	Exclude	Include
38	Seldane	Nedocromil	Exclude	Include
80	Seldane, Pyribenzamine	Nedocromil	Exclude	Include
83	Seldane, Naphcon A	Nedocromil	Exclude	Include
100	Chlor-Tripolon, Visine	Nedocromil	Exclude	Include
130	Phenergan	Nedocromil	Exclude	Include
133	Omade	Nedocromil	Exclude	Include
140	Seldane	Nedocromil	Exclude	Include
14	Stopped using drops	Placebo	Exclude	Include
22	Prednisolone	Placebo	Exclude	Include
35	Dristan	Placebo	Exclude	Include
39	Moved, Seldane	Placebo	Exclude	Include
42	Prednisolone	Placebo	Exclude	Include
45	Opticrom	Placebo	Exclude	Include
71	Prednisolone Hismanal Opticrom	Placebo	Exclude	Include
75	Prednisolone	Placebo	Exclude	Include
76	Prednisolone & Benadryl	Placebo	Exclude	Include
81	Omade	Placebo	Exclude	Include
86	Tavist	Placebo	Exclude	Include
93	Visine	Placebo	Exclude	Include
99	Benadryl	Placebo	Exclude	Include
102	Dimetapp, Visine	Placebo	Exclude	Include
114	Prednisolone	Placebo	Exclude	Include
143	Visine	Placebo	Exclude	Include

**Table of Withdrawals and Exclusions from the Analysis:**

Pt N	Reason	Tx	Clinic	Sponsor Excluded Analysis	Type	Per Protocol Observed Cases	ITT LOCF
43	Non cooperation	P		Safety & Efficacy	W	Exclude	Include
78	Non cooperation	P		Safety & Efficacy	W	Exclude	Include
128	Taking Hismanal for a stuffy nose	P		Safety & Efficacy	W	Exclude	Include
3	Consent withdrawn - patient had another eye disease present	N		Safety & Efficacy	W	Excluded No Data	Excluded No Data
44	Consent withdrawn - not known if patient used test treatment	N		Safety & Efficacy	E	Excluded No Data	Excluded No Data
5	Patient has another eye disease (associated chronic follicular conjunctivitis. Possibly related to make-up material).	P	reenbau	Safety & Efficacy	E	Excluded No Data	Excluded No Data
32	Consent withdrawn - no eye symptoms.	P	reenbau	Safety & Efficacy	E	Excluded No Data	Excluded No Data
72	No reason stated - only baseline week completed.	N	Marshall	Safety & Efficacy	E	Excluded No Data	Excluded No Data
74	Patient had other eye condition present.	N	Marshall	Safety & Efficacy	E	Excluded No Data	Excluded No Data
97	Consent withdrawn - moved outside trial area.	N	Marshall	Safety & Efficacy	E	Excluded No Data	Excluded No Data
77	Patient had other eye condition present (dry eyes)	P	Marshall	Safety & Efficacy	E	Excluded No Data	Excluded No Data
94	Consent withdrawn - scheduling interferes with working hours and unable to adjust.	P	Marshall	Safety & Efficacy	E	Excluded No Data	Excluded No Data
117	Non-compliance - study visits and diary cards	N	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
125	Non-compliance - study drug regimen. Not known if patient used test treatment. Also taking Hismanal during baseline.	N	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
126	Non-compliance - study drug regimen and study visits. Not known if patient used test treatment.	N	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
141	Consent withdrawn - wears contact lenses. Refuses to stop wearing them during study.	N	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
144	Non-compliance - study visits. Not known if used test treatment.	N	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
146	Taking Seldane during baseline	N	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
127	Non-compliance - study visits. Not known if used test treatment.	P	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
132	Non-compliance - study drug regimen and diary cards. Not known if patient used test treatment.	P	Alexande	Safety & Efficacy	E	Excluded No Data	Excluded No Data
142	Non-compliance - lost to follow up.	lace	Alexande	Safety & Efficacy		Excluded No Data	Excluded No Data

**Reviewer Comment:** *Not acceptable. Raw data should be provided for the eighteen excluded patients so that an intent-to-treat analysis with last observation carried forward can be conducted. The sponsor does not provide information on the length of time excluded patients used the test treatment, or if they started the test treatment. For the purposes of this review, whenever raw data was supplied by the sponsor, was analyzed with exclusions treated by both an intent-to-treat, last-observation-carried forward, and per-protocol, observed cases methodology.*

### Data Set Analyzed for Diary Card Variables

Any diary card which was completed for less than four days during the analyzed periods was excluded from the analysis. Diary card eye symptoms on the three days of a patient taking oral prednisolone and the following three days were not to be included in the analysis.

**Table of Sponsor's Withdrawals and Exclusions for Diary Card Variables**

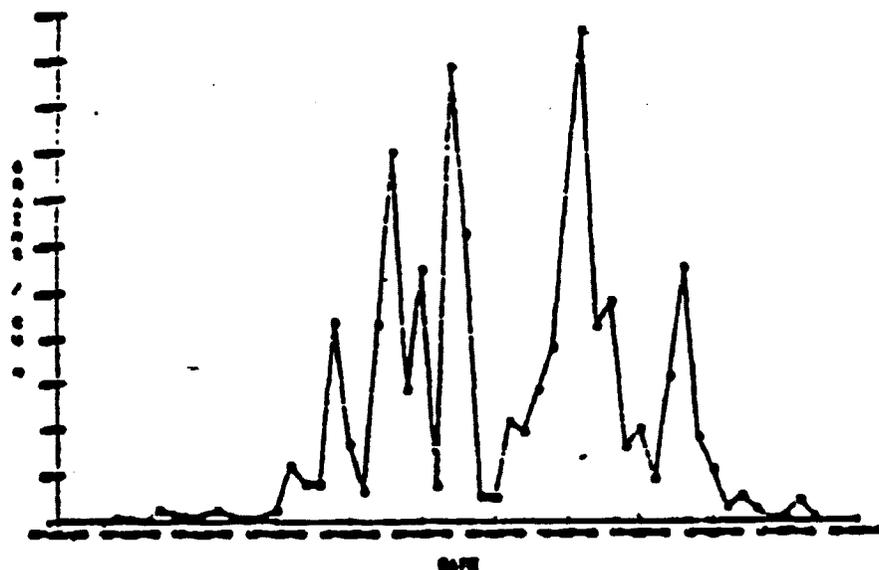
Pt No	Reason	Treatment	Sponsor Excluded Analysis	Per Protocol Observed Cases	ITT LOCF
33	Failed to record accurately for general eye condition.	Nedocromil	Diary	Include	Include
16	Recorded general eye condition intermittently throughout study	Nedocromil	Diary	Include	Include
80	Recorded general eye condition intermittently throughout study	Nedocromil	Diary	Exclude only missing data	Include
128	Recorded general eye condition intermittently throughout study	Placebo	Diary	Exclude only missing data	Include
114	Data excluded between 18 August and 11 September for taking oral prednisolone with the test treatment.	Placebo	Diary	Exclude only missing data	Include
71	Data excluded between 29 August and 7 September for taking oral prednisolone with the test treatment.	Placebo	Diary	Exclude only missing data	Include
39	Left the trial area between 4 September and 7 September	Placebo	Diary	Exclude only missing data	Include
14	Stopped taking treatment on 7 September	Placebo	Diary	Exclude only missing data	Include

**Reviewer Comment:** *Raw data is available for the above-listed patients except for the excluded time periods listed in the table above for patients 114, 71, 39, and 14. For the purpose of this review this data will be included in the intent to treat analysis with last observation carried forward. Only the blocked data will be excluded from the per protocol analysis.*

APPROVED FOR SIGNATURE  
ON 08/11/14

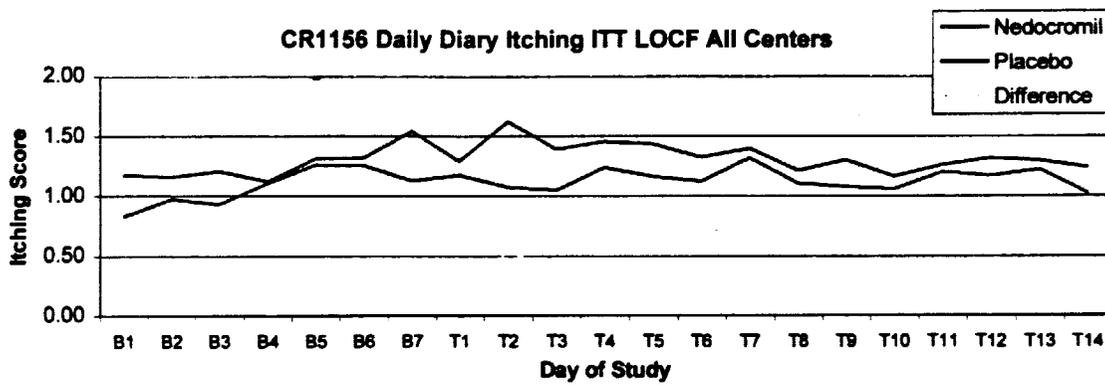
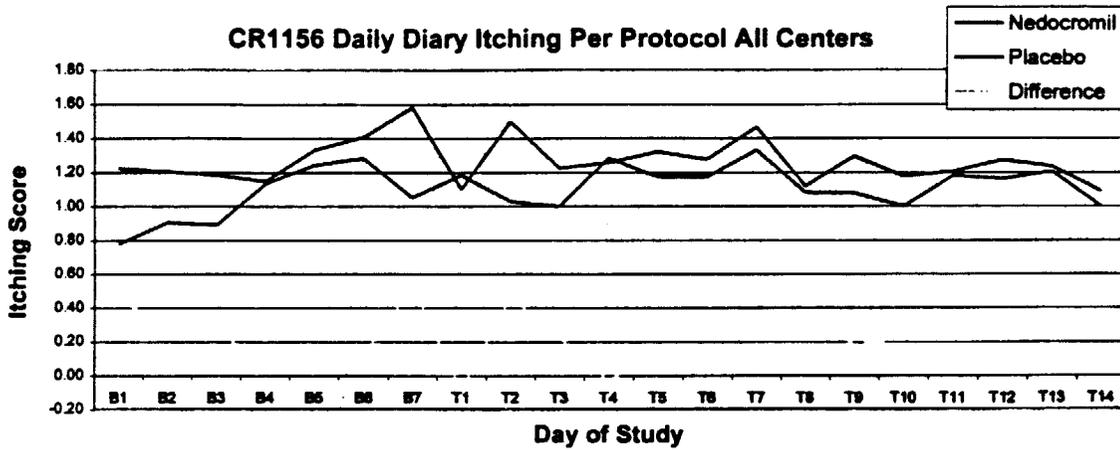
**Efficacy:**

Ragweed pollen counts were recorded daily in the Southwestern Ontario area from 1 August to 19 September 1986. The periods of highest pollen challenge occurred between 20 and 26 August and between 31 August and 10 September. During the entire period of 20 August to 10 September, the pollen count fell below 50 grains/m<sup>3</sup> on eight days.

**Scan of Sponsor's Graph of Daily Pollen Counts**

Location	Sponsor Peak Pollen Period 1	Mean Pollen Count	Sponsor Peak Pollen Period 2	Mean Pollen Count	Start Tx	Minimum # of Days before Peak Pollen season	# of Patients	Medical Officer Peak Pollen Period	Medical Officer Baseline Period
Hamilton	8/20 to 8/26	107.1 grs/m <sup>3</sup>	8/31 to 9/10	79.1 grains/m <sup>3</sup>	8/18 to 8/19	1 to 2	44	8/20 to 9/2	8/13 to 8/19
St Catherine's	8/20 to 8/26	107.1 grs/m <sup>3</sup>	8/31 to 9/10	79.1 grains/m <sup>3</sup>	8/15 to 8/17	3 to 5	31	8/20 to 9/2	8/13 to 8/19
Niagra Falls	8/20 to 8/26	107.1 grs/m <sup>3</sup>	8/31 to 9/10	79.1 grains/m <sup>3</sup>	8/15	5	25	8/20 to 9/2	8/13 to 8/19

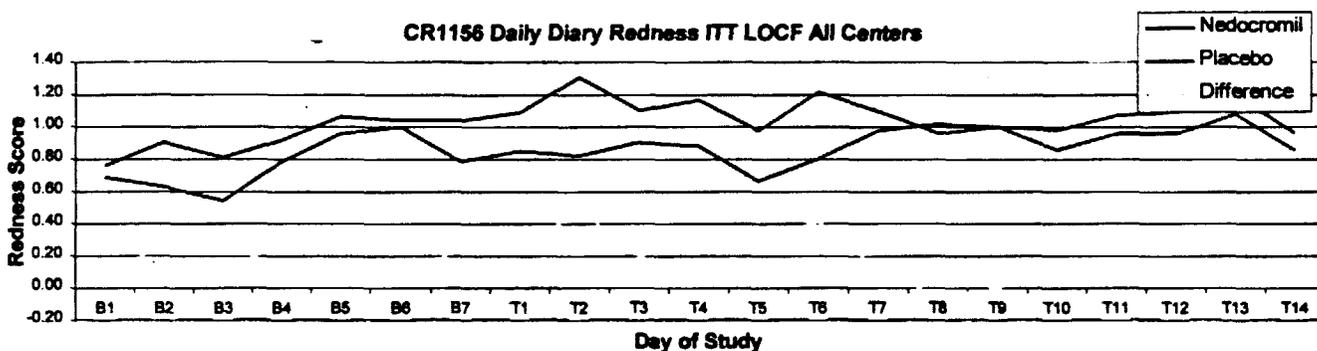
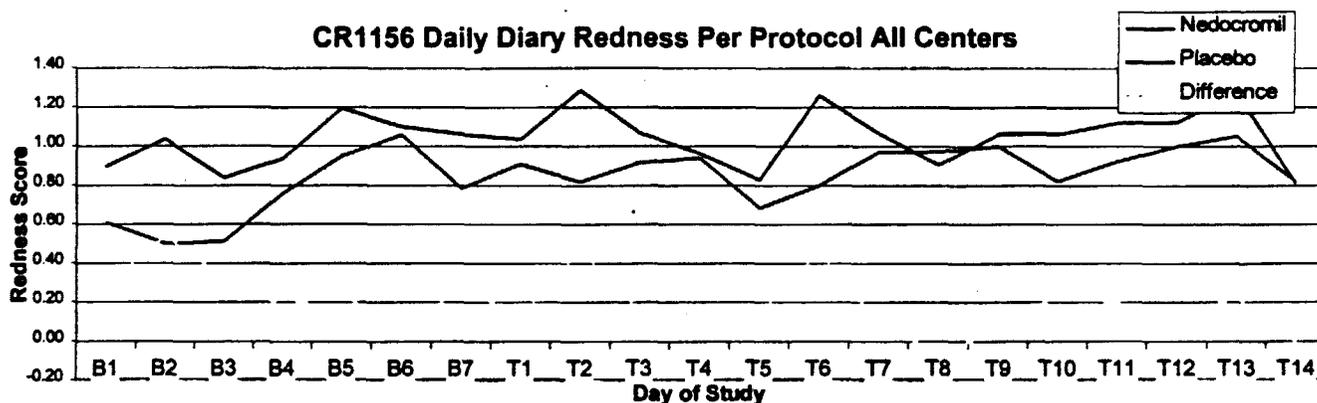
**Reviewer Comment:** *Not Acceptable. The raw pollen count data are not provided. The graphic representation of the pollen count is illegible. The sponsor has been unable to provide a legible copy. The sponsor has not justified the choice of the peak pollen period. The peak pollen count is recorded to profile a pollen season. It is not representative of an individual patient's experience. Therefore it is not acceptable to exclude some data by dividing the peak pollen period. The sponsor defined the baseline period as the 7 day period prior to administration of study drug. For purposes of this review, the reviewer defines the 14-day period of 20 August to 2 September 1986, as the peak pollen period with the preceding seven day period between 13 August and 19 August as the baseline period.*



**Statistical Analysis of CR1156 Itching:**

Itching Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust Baseline	Difference
Placebo	1.28	35	1.23	34	-0.016				
Nedocromil	1.05	39	1.13	39	0.08	Not done	0.776	0.357	0.1
Itching ITT LOCF									
Placebo	1.25	53	1.34	53	0.084				0.19
Nedocromil	1.12	49	1.15	49	0.038	Not done	0.575	0.185	

**Reviewer Comment:** *Nedocromil failed to show efficacy in reducing itching in CR1156.*



**Statistical Analysis of CR1156 Redness**

Redness Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust Baseline	Difference
Placebo	0.95	35	1.02	34	0.1	Not done	0.7	0.262	0.13
Nedocromil	0.75	39	0.89	39	0.15				
<b>Redness ITT</b>									
Placebo	0.93	53	1.1	53	0.16	Not done	0.443	0.096	0.24
Nedocromil	0.78	49	0.86	49	0.08				

**Reviewer Comment:** *Nedocromil fails to show efficacy in reducing redness in study CR1156.*

APPROVED BY  
C. CRONIN

**Adverse Events:**

Table of "Clinical Events" reported during the study:

Experience	Nedocromil	Vehicle
Stuffy Nose	19	25
Running Nose	15	11
Sneezing	9	8
Itchy Nose	3	4
Tinitis	5	4
Nasal Congestion	14	18
Asthma 'tight chest'	5	0
Tonsillitis	3	2
Itchy mouth	1	0
Congested ears	1	0
Puffy face	1	0
Gastric symptoms	1	2
Hives	0	1
Headache, migraine	0	3
Kidney infection	0	1
Crohn's disease	0	1
Dysmenorrhea	1	0
Pregnancy	1	0

**Reviewer's Comments:** *The applicant should identify the outcome of the pregnancy.*

Table of "Side Effects" reported during the study:

Experience	Nedocromil	Vehicle
Aftertaste	7	9
Stinging eyes	8	7
Burning eyes	7	5
Sore eyes	2	2
Itchy eyes	0	5
Eyes cold	0	1
Eyes puffy	1	1
Red eyes	0	1
Eyes watering	1	0
Eyes blurring	0	1
Eyes dry	0	2
Eye discharge	0	2
Periorbital pain	1	0
Headache (sinus)	1	0

**7.1.8 Study #8 Protocol #CR1891****Title: A Double-Blind Group Comparative Multicenter Study to Compare the efficacy and Tolerability of Nedocromil Sodium 2% Aqueous Eye Drops in the Treatment of Seasonal Allergic Conjunctivitis Due to Ragweed Pollen**

**Objective:** To compare the efficacy and tolerability of nedocromil sodium, terfenadine and vehicle in the treatment of seasonal allergic conjunctivitis due to ragweed pollen.

**Duration:** 24 July 1989 and 16 August 1989.

**Study design:** This study was designed as a double-blind, double-dummy, group comparative multi-center study with patients randomly allocated to receive either nedocromil sodium eye drops and vehicle tablets or terfenadine and vehicle eye drops or vehicle eye drops and vehicle tablets for four weeks, after completion of a 7-14 day baseline period.

Investigator	Address	Country	Number Randomized	Number Completed
Dr. M Alexander	6150 Valley Way, Suite 207 Niagra Falls, Ontario, L2E1Y3	Canada	70	70
Dr. M. Rosen	333 Wilson Avenue, Suite 405 Downsview, Ontario, M3H1T2	Canada	80	78
Dr. J. Dolovich	[REDACTED] Hamilton, Ontario	Canada	76	76
Dr. W.B.C. Yang Dr. M.A.Drouin	[REDACTED] 1053 Carling Avenue Ottawa, Ontario, K1Y4EG	Canada	44	44
		Total	270	268

**Study Plan:**

- The active drug solution: Same as study CR1156  
One drop was given to each eye, twice daily.
- The Vehicle solution: Same as study CR1156  
One drop was given drop to each eye, twice daily.
- Terfenadine 60 mg tablets and matching vehicle tablets, one to be taken twice daily.

**Reviewer Comment:** *Acceptable.*

**Concomitant Medication:****Permitted**

- Hypromellose eye drops (artificial tears) was the only permitted addition to study drug.
- Topical nasal medication (eg sodium cromoglycate, beclomethasone dipropionate) could be used to control rhinitic symptoms.

**Table of Number of subjects (planned and analyzed):**

	Sponsor Analysis				Medical Officer Analysis			
	Nedocromil	Terfenadine	Placebo	Total	Nedocromil	Terfenadine	Placebo	Total
Planned								
*Data returned for analysis	90	89	90	269	89	89	90	268
*Excluded	1	0	0	1				2
Analyzed: Efficacy	86	86	89					
Analyzed: Safety	89	89	90					
Withdrawals				12	5	5	3	13
Lack of efficacy	4	2	2	8	4	2	2	8
Suspected adverse reaction	1	1	1	3	1	1	1	3
Severe concurrent illness	0	1	0	1	0	1	0	1
Non compliance					0	1	0	1
Protocol Violations					10	9	10	29
Analyzed: Efficacy Per Protocol					79	80	80	239
Analyzed: Efficacy ITT LOCF					89	89	90	268

**Table Accounting for Missing Data:**

NSO Missing Data	Reason	Data Available	Case Report Form Available
331		None	No
380		None	No
311	Lack of effect	Baseline & 6d tx	No
338	Lack of effect	Baseline	No
376	Lack of effect	Baseline & 7d tx	No
405	Suspected Adverse Rxn	1 day baseline	No
419	?	Baseline & 9d tx	No
430	?	Baseline & 9d tx	No
350	?	Baseline & 6d tx	No
Placebo Missing Data	Reason	Data available	Case Report
309	Lack of Effect	Baseline only	No
349	Lack of Effect	Baseline & 7d tx	No
441	Suspected Adverse Reaction	Baseline only	No
328	Wrong amount study drug	Baseline & 8d tx	No
349	Visit at wrong time	Baseline & 7d tx	No
Terfenadine missing data	Reason	Data Available	Case Report
209	Suspected Adverse Reaction	Baseline & 10 d tx	No
356	Lack of effect	Baseline & 9d tx	No
425	Severe Concurrent Illness	Baseline & 7d tx	No
434	Lack of effect	Baseline	No
413	Possible Missed Visit	Baseline & 10 d tx	No

**Demographics:**

Subjects		Nedocromil	Terfenadine	Placebo	Total
Gender					
	Female	49	49	57	155
	Male	40	40	33	113
Mean Age (Years)		32.7	33.1	33.2	

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

APPROVED FOR SIGNATURE  
 OF [Name]

**Study Flow Chart**

Weeks		0	1	2	3	4	5
Visits		1	2		3		4
Clinical Assessment		X	X		X		X
Assessment form		X	X		X		
Diary Card		X	X		X		X
Unusual Symptoms			X		X		X
Patients Opinion					X		X
Trialist's Opinion							X
Speed of onset							X
Duration of effect							X
Withdrawal form							X*
Treatment	Nedocromil gtts BID OU + Placebo tablets		X	X	X	X	X
	Placebo gtts BID OU + Terfenadine tablets		X	X	X	X	X
	Placebo gtts BID OU + placebo tablets		X	X	X	X	X

\*To be completed if patient withdraws from study prior to conclusion of study.

**Subject Population:**

Patients had a history of seasonal allergic conjunctivitis, and met the inclusion and exclusion criteria.

**Inclusion Criteria**

- Males and females, aged 12 years or over, who were able to comply with test procedures.
- Patients with a positive skin test to ragweed and a history of being symptomatic to no other allergens that affected the eye between 5 August to 30 September.
- Patients who have been treated for allergic conjunctivitis to ragweed for at least two previous seasons in which their immunotherapy has not been altered.
- Positive skin test to ragweed pollen may already have been established in previous 12 months.
- Patients with concomitant rhinitis or asthma may be included
- Patients had to remain in the clinic area for the duration of the study.
- Patients or their parents had to give written informed consent to the study.

**Exclusion Criteria**

- Patients with any additional eye disease which might have interfered with the study.
- Patients with significant renal, hepatic, cardiovascular or hematopoietic diseases.
- Patients who would have worn contact lenses during the course of the study.
- Patients who were undergoing routine immunotherapy for the first time.
- Patients who have undergone routine immunotherapy and have not demonstrated allergic conjunctivitis in a subsequent season.
- Patient who will require systemic corticosteroids and/or any systemic antihistamines.
- Patients who require any other medications with antihistaminic effects (e.g. H2 antagonists, psychotropic agents).
- Patients who were pregnant or nursing, at risk of pregnancy or not following adequate contraceptive techniques.

**Reviewer Comment:** *Acceptable.*

**Criteria for evaluation:**

**Efficacy:**

**Assessments by the investigator**

An initial assessment will be carried out prior to trial entry. The patients' clinical history and characteristics will be recorded and an assessment of current eye symptoms made. An assessment of current eye symptoms will be made at each subsequent visit. After a total of four weeks treatment, a final clinical assessment will be made. The clinician's opinion of the test treatment will be recorded.

The clinician's opinion of treatment will be quantified and at each assessment the patient will give his/her opinion of the test treatment using the scale:

- 0 = No symptoms
- 1 = Slight symptoms
- 2 = Moderate symptoms
- 3 = Severe symptoms

**Assessments by Patients**

*Throughout the four week treatment period the patients will record on daily diary cards the eye symptoms outlined above using the scale:*

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Very severe symptoms

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**Primary Variables**

- **Diary card symptoms scores**
- **Use of rescue medication during the peak pollen period**
- **Patient's opinion of treatment expressed at the end of the study**

**Secondary Variables**

- **Diary card symptoms scores analyzed in week-long blocks during the total study period**
- **Total concomitant medication usage throughout the study period**
- **Clinician's overall opinion of treatment given at the end of the study**
- **Speed of onset and duration of effect of test treatment given at the end of the study**

**Safety:** Safety is assessed by comparing the incidence of adverse reaction as recorded on the clinical assessment forms.

**Recording of Unusual Symptoms**

At Visit 2,3 and the final assessment or at the time of withdrawal from the study, any unusual symptoms will be inquired for, assessed and recorded by the trialist.

**Reviewer Comment:** *Acceptable.*

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**Withdrawals and Exclusions:** Patients were free to withdraw or to be withdrawn from the study at any time.

**Table of Withdrawals and Exclusions:**

Pt No	Duration of Treatment	Reason	Treatment	Clinic	Medical Officer Per Protocol Observed Cases	Medical Officer ITT LOCF
311	10	Lack of Effect of Treatment	Nedocromil	Rosen	Include	Include
338	5	Lack of Effect of Treatment	Nedocromil	Rosen	Include	Include
358	14	Lack of Effect of Treatment	Nedocromil	Rosen	Include	Include
376	14	Lack of Effect of Treatment	Nedocromil	Rosen	Include	Include
405	4	Suspected Adverse Reaction	Nedocromil	Yang/Drouin	Include	Include
209	24	Suspected Adverse Reaction	Terfenadine	Dolovich	Include	Include
325	?	Failure to Attend	Terfenadine	Rosen	Include	Include
356	16	Lack of Effect of Treatment	Terfenadine	Rosen	Exclude	Include
425	16	Severe Concurrent Illness	Terfenadine	Yang/Drouin	Include	Include
434	13	Lack of Effect of Treatment	Terfenadine	Yang/Drouin	Include	Include
309	8	Lack of Effect of Treatment	Placebo	Rosen	Include	Include
349	14	Lack of Effect of Treatment	Placebo	Rosen	Include	Include
441	7	Suspected Adverse Reaction	Placebo	Yang/Drouin	Include	Include

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**Reviewer Comment:** *Two patients from Dr. Rosen's center were excluded from the study on account of non-compliance (failure to take test treatment). (Pts 331 and 380). The type of analysis from which patients were excluded by the sponsor and by the medical officer is indicated in the table of Withdrawals and Exclusions and in the three tables of Protocol Deviations below.*

Table of Protocol Deviations--Nedocromil

Pt No	Reason	Excluded Analysis	Medical Officer Per Protocol Observed Cases	Medical Officer ITT LOCF
106	Took a steroid throughout the study	2-4 symptom scores, opinions, speed/duration of action, peak pollen period	Exclude	Include
142	Took a steroid prior to visit 2	Visit 2 symptoms scores	Exclude	Include
205	Took a steroid throughout the study	Visit 2-4 symptom scores, peak pollen period	Exclude	Include
206	Took antihistamines prior to visit 2	Visit 2 symptoms scores	Exclude	Include
219	Visit 4 eight days after stopping test treatment	Visit 4 symptom scores	Include	Include
227	Visit 4 20 days after visit 3, only drops taken 5 days prior to visit 4	Visit 4 symptom scores	Include	Include
231	Took a steroid throughout the study	Visits 2-4 symptom scores, opinions, speed/duration of action, peak pollen period	Exclude	Include
238	Visit 3 18 days after Visit 2	Visit 3 symptom scores	Include	Include
259	Took an antihistamine prior to visit 2	Visit 2 symptoms scores	Exclude	Include
268	Took a steroid during the study	Visit 4 symptom scores, peak pollen period	Exclude	Include
302	Visit 4 six days after stopping test treatment	Visit 4 symptom scores	Include	Include
306	Took a steroid between Visits 2 & 3	Visit 3 symptom scores, peak pollen period	Exclude	Include
338	Visit 3 ten days after stopping test treatment. Did not attend Visit 4	Visit 3 symptom scores	Include	Include
342	Took a steroid throughout the study	Visits 2-4 symptom scores, opinions, speed/duration of action, peak pollen period	Exclude	Include
359	Took 2 test drops a day, not four throughout the study	Visits 3 and 4 symptom scores, opinions, speed/duration of action, peak pollen period	Exclude	Include
371	Visit 3 eight days after Visit 2, Visit 4 25 days after Visit 3	Visits 3 and 4 symptom scores, peak pollen period	Include	Include
405	Visit 3 three days after Visit 2, Visit 4 same day as visit 3	Visits 3 and 4 symptom scores, opinions, speed/duration of action, peak pollen period	Include	Include
419	Visit 4 nine days after Visit 3	Visit 4 symptom scores	Include	Include
430	Visit 4 ten days after Visit 3	Visit 4 symptom scores	Include	Include

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Table of Protocol Deviations--Terfenadine

Pt No	Reason	Sponsor Excluded Analysis	Medical Officer Per Protocol Observed Cases	Medical Officer ITT LOCF
161	Took a steroid throughout the study	Visits 2-4 symptom scores, opinions, speed/duration	Excluded	Included
209	Took a steroid throughout the study, Visit 4 days after stopping test treatment	Visits 2-4 symptom scores, opinions, speed/duration	Excluded	Included
220	Only test drops taken between Visits 2 and 3, Visit 4 22 days after Visit 3	Visit 3 symptom scores and opinions, Visit 4 symptom scores.	Excluded	Included
236	Only test drops taken three days prior to Visit 4	Visit 4 symptom scores, last day of peak pollen period	Excluded	Included
305	Visit 3 18 days after Visit 2	Visit 3 symptom scores	Included	Included
308	Test treatment not taken on three days prior to Visit 4	Visit 4 symptom scores, last 2 days of peak pollen period	Excluded	Included
310	Visit 3 ten days after Visit 2	Visit 3 symptom scores	Included	Included
315	Took a steroid throughout the study	Visits 2-4 symptom scores, opinions, speed/duration of action, peak pollen period	Excluded	Included
334	Took an antihistamine between Visits 2 and 3, Visit 4 five days after stopping test treatment	Visit 3 symptom scores, Visit 4 symptom scores, peak pollen period	Excluded	Included
355	Took an antihistamine during the study	Visits 2-4 symptom scores, peak pollen period	Excluded	Included
356	Took an antihistamine prior to Visit 4, Visit 4 two days after Visit 3	Visit 4 symptom scores, last 2 days of peak pollen period	Excluded	Included
377	Visit 3 20 days after Visit 2, Visit 4 12 days after Visit 3	Visits 3 and 4 symptom scores	Included	Included
413	Visit 4 nine days after Visit 3	Visit 4 symptom scores	Included	Included
425	Visit 4 on same day as Visit 3	Visit 4 symptom scores and opinions	Included	Included
434	Visit 4 on same day as Visit 3	Visit 4 symptom scores and opinions	Included	Included

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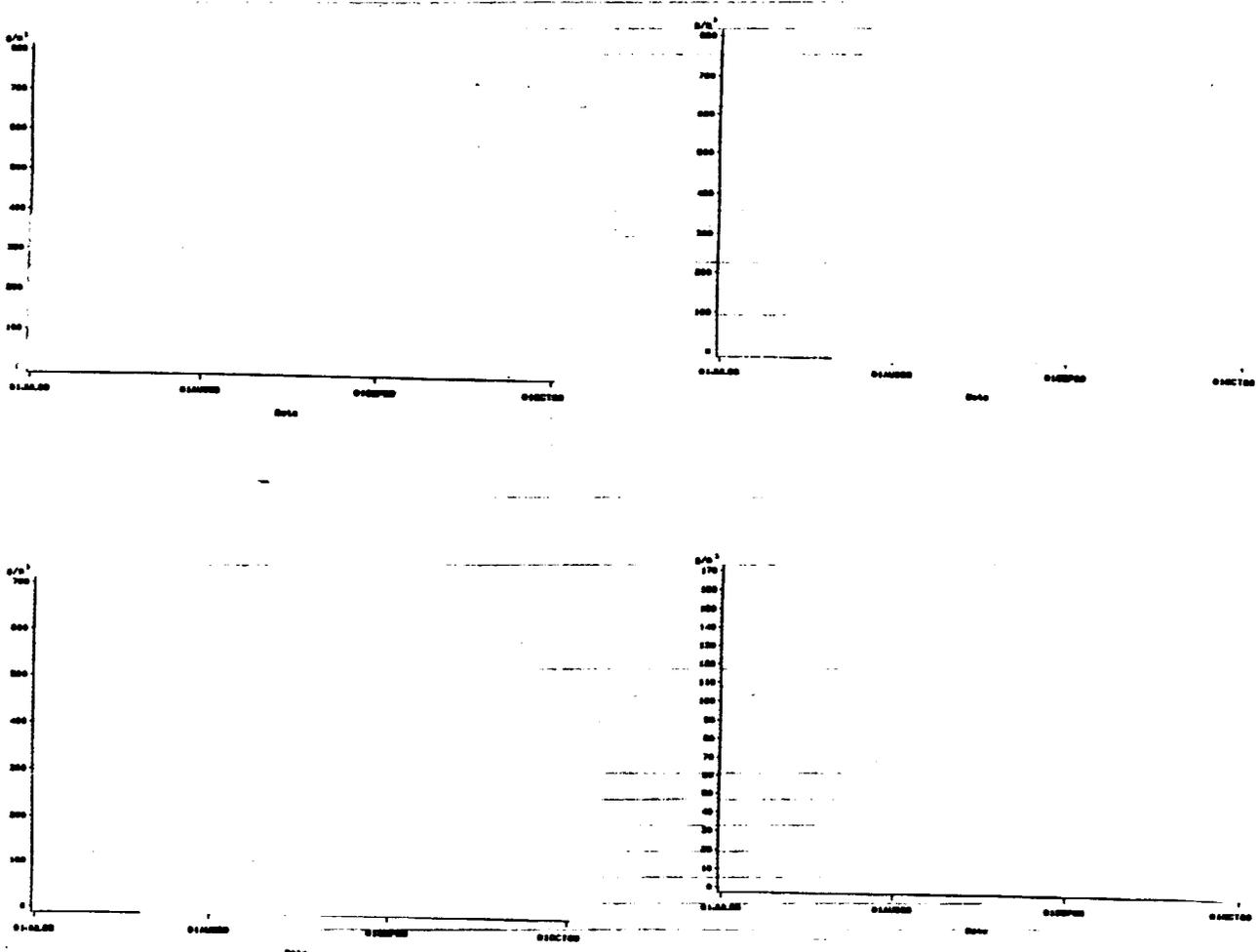
Table of Protocol Deviations: Vehicle

Pt No	Reason	Treatment	Sponsor Excluded Analysis	Per Protocol Observed Cases	ITT LOCF
117	Visit 4 three days after stopping test treatment	Placebo	Visit 4 symptom scores	Include	Include
141	Visit 3 then days after Visit 2, Visit 4 4 days after stopping test treatment	Placebo	Visits 3 and 4 symptom scores	Include	Include
149	Took an antihistamine prior to Visit 4	Placebo	Visit 4 symptom scores, last 2 days of peak pollen period	Exclude	Include
223	Visit 4 three days after stopping test treatment	Placebo	Visit 4 symptom scores	Include	Include
241	Took a steroid during the study	Placebo	Visits 2 and 4 symptom scores, peak pollen period	Exclude	Include
253	Took an antihistamine prior to Visit 4	Placebo	Visits 2 and 3 symptom scores, peak pollen period	Exclude	Include
274	Visit 3 22 days after Visit 2	Placebo	Visit 3 symptom scores	Include	Include
303	Took an antihistamine and immunotherapy during the study	Placebo	Visits 2-4 symptom scores, peak pollen period	Exclude	Include
313	Took an antihistamine between Visits 3 and 4	Placebo	Visit 4 symptom scores, peak pollen period	Exclude	Include
328	Took 2 test drops a day not four throughout the study	Placebo	Visits 3 and 4 symptom scores, opinions, speed/duration of action, peak pollen period	Exclude	Include
349	Visit 3 six days after stopping test treatment. Did not attend Visit 4	Placebo	Visit 3 symptom scores	Include	Include
357	Took two steroids throughout the study	Placebo	Visits 2-4 symptom scores, opinions, speed/duration of action, peak pollen period	Exclude	Include
358	Visit 3 eight days after Visit 2	Placebo	Visit 3 symptom scores	Include	Include
363	Took a steroid prior to visit 2	Placebo	Visit 2 symptom scores	Exclude	Include
364	Visit 4 seven days after Visit 3	Placebo	Visit 4 symptom scores	Include	Include
379	Took an antihistamine between Visits 2 and 3	Placebo	Visit 3 symptom scores, peak pollen period	Exclude	Include
417	Only test drops taken 3 days prior to Visit 4, Visit 4 20 days after visit 3	Placebo	Visit 4 symptom scores, last day of peak pollen period	Exclude	Include
433	Visit 4 on same day as Visit 3	Placebo	Visit 4 symptom scores and opinions	Include	Include
441	Visit 4 on same day as Visit 3, seven days after stopping test treatment	Placebo	Visits 3 and 4 symptom scores, Visit 4 opinion	Include	Include

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Efficacy:

# BEST POSSIBLE COPY



**Reviewer Comment:**

*Acceptable: Although the raw pollen data is not provided, clearly legible graphs of daily pollen counts support the sponsor's choice of a peak pollen period.*

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Location	Sponsor Peak Pollen Period	Mean Pollen count	Start Tx	Minimum # Days before Peak Pollen Period	# of Patients	Medical Officer Peak Pollen Period	Medical Officer Baseline Period
Niagra Falls	8/23 to 9/9	307.7	8/10 to 8/12	11	70	8/23 to 9/5	8/16 to 8/22
Downsview	8/23 to 9/9	307.7	8/10 to 8/11	12	80	8/23 to 9/5	8/16 to 8/22
Hamilton	8/23 to 9/9	54.4	8/9 to 8/16	7	76	8/23 to 9/5	8/16 to 8/22
Ottawa	8/23 to 9/9	295	8/10 to 8/17	6	44	8/23 to 9/5	8/16 to 8/22

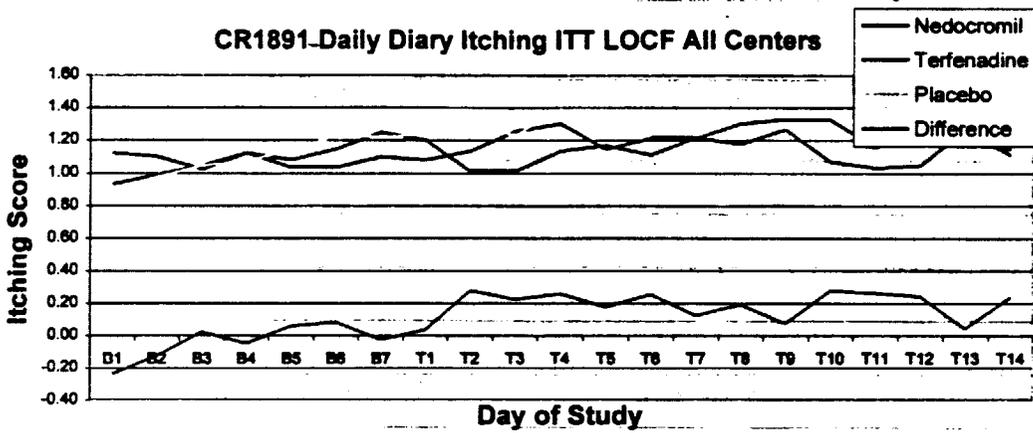
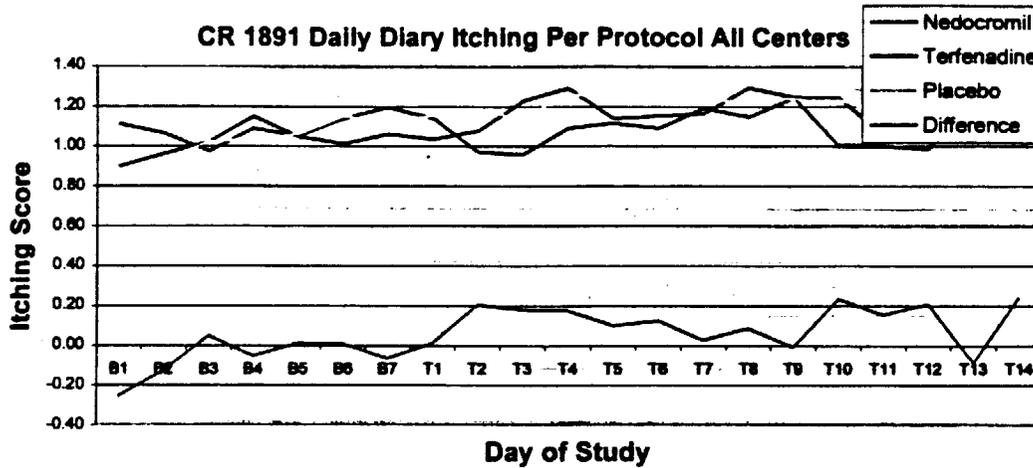
**Reviewer Comment:** *For the purpose of this review, the peak pollen period was taken as the 14-day period starting at the sponsor's designated peak pollen period. The baseline period was taken as the 7-day period just prior to the peak pollen period. The approximate number of days the subjects at each center received the test treatment prior to the peak pollen period is specified in the table above. In this study the majority of patients received the test treatment during the entire baseline period.*

## Adverse Events:

Table of "Unusual symptoms" reported during the study:

Nedocromil Pt #	Nedocromil Experience	Placebo Pt #	Placebo Experience	Terfenadine Pt #	Terfenadine Experience
344	Abdominal Discomfort	417	Kidney Stone	402	Rhinitis
306	Arthritis	274	Post op mouth pai	329	Headache
405	Chest congestion	426	Cold	411	Headache
260	Cough	253	Headache	261	Headache
221	Dry Eyes	217	Headache	225	Chest tightness
271	Ear Pain	264	Irritated eye	315	Asthma
271	Ear Surgery	258	Insomnia	308	Abdominal Pain
242	GI Flu	224	Headache	254	Sore throat
376	GI Upset	423	Cough	404	Drowsy
227	Headache	223	Cold	229	Headache
251	Headache	245	Dry Eyes	256	Rash
105	Headache	101	Headache	113	Headache
114	Headache	128	Headache	137	Headache
119	Headache	140	Headache	170	Headache
138	Headache	141	Headache	202	Stomach Upset
159	Headache	157	Headache	204	Sigmoidoscopy
219	Headache	207	Headache	220	Headache
260	Headache	246	Headache	261	Inflammation
276	Headache	274	Headache	322	Fatigue
327	Headache	407	Headache	377	Vomiting
330	Headache	408	Itchy Eyes	377	Abdominal Pain
410	Headache	428	Post op pain	413	Nausea
271	Insomnia	274	Throat infection	315	Rash
327	Itchy Eyes	407	Dizzy	377	Nausea
319	Itchy Eyes	346	Insomnia	336	Sleepy
206	Menstrual Pain	203	Swollen Eye	209	Nausea
405	Nervousness	426	Ear pain	409	Tooth Pain
260	Short of Breath	257	Headache	261	Stress
327	Sinus congestion	357	Diarrhea	361	Headache
319	Sore and burning eyes	353	Headache	336	Dizzy
430	Sore cheek			425	Nasal congestion
105	Sore Muscles	116	Headache	115	Headache
327	Sore Throat	372	Drowsy	375	Headache
235	Stinging on Drug Installation	223	Sore throat	236	Cold
410	Swollen Right Eye	441	Eye irritation	413	Dry Mouth
205	Taste Perversion	158	Headache	209	Headache
319	Taste Perversion	353	Heart burn	340	Pimples
242	Ulcer Attack	226	Headache	256	Headache
330	Upset stomach	408	Nasal congestion	377	Hypertension
260	Vaginal Yeast Infection	246	Headache	261	Pain
430	Watery Eye			425	Cold
				437	Cold
				437	Swollen Eye
				439	Wheezing
				439	Cough

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ON ORIGINAL

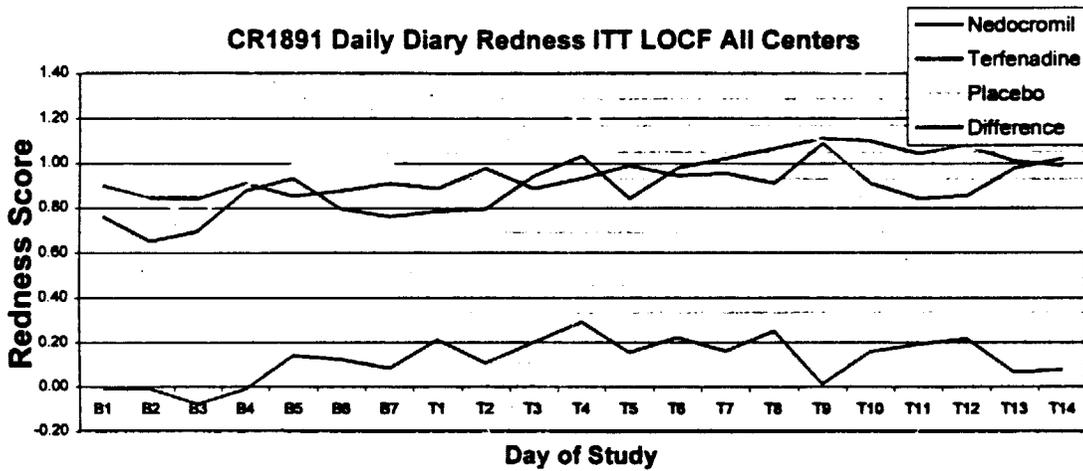
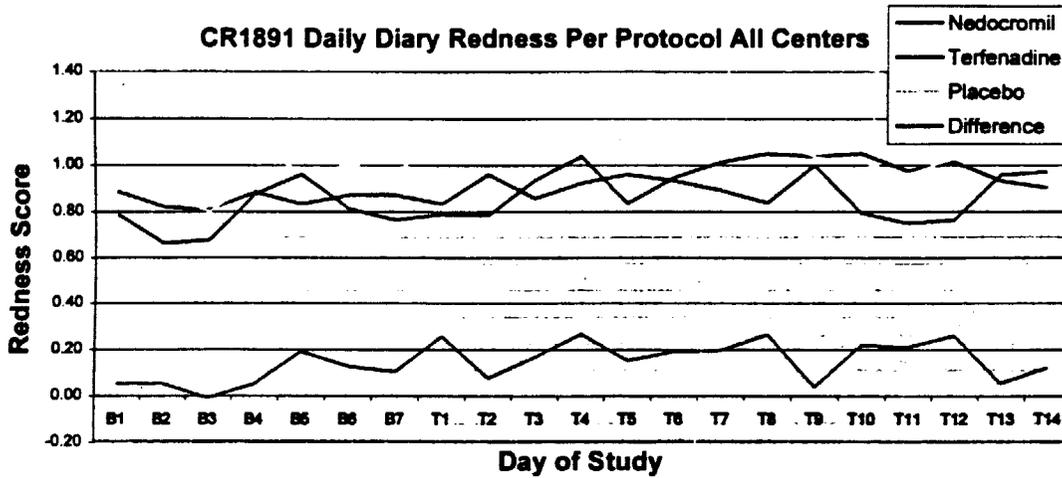


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**Study 1891 Statistical Analysis Itching**

Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust Baseline	Difference
Placebo	1.03	80	1.2	78	0.21				
Nedocromil	1.1	79	1.12	77	0.02	Not done	0.013	0.354	0.08
Terfenadine	1.02	80	1.19	80	0.16	Not done	0.112	0.49	0.01
ITT									
Placebo	1.07	90	1.29	88	0.24				
Nedocromil	1.12	89	1.13	87	0.007	Not done	0.003	0.195	0.16
Terfenadine	1.04	89	1.22	89	0.188	Not done	0.142	0.434	0.07

APPEARS THIS WAY  
ON ORIGINAL



**Study 1891 Statistical Analysis Redness**

Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust Baseline	Difference
Placebo	0.94	80	1.08	78	0.15				
Nedocromil	0.85	79	0.91	77	0.06	Not done			0.17
Terfenadine	0.79	80	0.97	80	0.18	Not done	0.095	0.167	0.11
ITT									
Placebo	0.91	90	1.16	88	0.21				
Nedocromil	0.88	89	0.95	87	0.06	Not done	0.03	0.197	0.21
Terfenadine	0.78	89	0.96	89	0.19	Not done	0.359	0.23	0.2

**7.1.9 Study #9 Protocol #CR1242****Title: A Multicenter Double-Blind Group Comparative Study of Nedocromil Sodium 2% Eye Drops and Placebo in the Treatment of Seasonal Allergic Conjunctivitis**

**Objectives:** Same as study CR1156 with the additional objective: To evaluate 2% nedocromil sodium eye drops vs. matching vehicle eye drop in the prevention of allergic conjunctivitis symptoms when the study drug is begun before environmental pollen challenge.

**Duration:** 28 April 1987 to 18 May 1987

**Study design:** Randomized, double-blind, group comparative multi-center study with patients receiving either nedocromil sodium eye drops or vehicle eye drops. Patients were to begin treatment up to two weeks before environmental pollen challenge during the peak pollen period. The rationale for prevention of allergic conjunctivitis symptoms relies on the hypothesis that nedocromil sodium may stabilize the mast cell in the ocular tissue.

**Table of Investigators**

Investigator	City	Country	# Randomized	# Completed
Dr. Leino	Kuopio	Finland	30	29
Dr. Jaanio	Mulken, Helsinki	Finland	14	14
Dr. Koivunen	Konvala, Helsinki	Finland	22	22
Dr. Carlson	Vantaa, Helsinki	Finland	30	27
Dr. Takalo	Oulu	Finland	31	30
		Total	127	122

APPEARS THIS WAY  
ON ORIGINAL

**Reviewer Comment:** *The sponsor should provide data regarding those patients randomized as well as those completing the study.*

**Study Plan:** Same as study CR1156

APPEARS THIS WAY  
ON ORIGINAL

**Concomitant Medication:**Permitted

- Otrivine-antihistatin for ocular escape therapy
- 2% sodium cromoglycate nasal spray (Rynacrom) for rhinitis symptoms

Not Permitted

- Any other topical eye drops
- Any other antihistamines

**Number of subjects (planned and analyzed):**

	Sponsor Analysis			Medical Officer Analysis		
	Nedocromil	Placebo	Total	Nedocromil	Placebo	Total
Planned			120			120
Unaccounted Randomization #						
*Data returned for analysis				64	63	127
Withdrew consent prior to receiving study drug			1			1
Entered	64	62	126	64	62	126
Excluded	3	1	4	3	1	4
Tx failure				1	0	1
Concurrent illness				0	1	0
Non compliance				2	0	2
Analyzed: Efficacy	61	61	122			
Analyzed: Safety	64	62	126	64	62	126
Withdrawals				7	12	19
Tx failure				3	6	9
Concurrent illness				0	2	2
Non compliance				3	4	7
Adverse Events				1	0	1
Protocol Violations				14	13	25
Analyzed: Efficacy per Protocol				46	46	92
Analyzed: Efficacy ITT LOCF				56	55	111

APPEARS THIS WAY  
ON ORIGINAL**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
21	Non-cooperation	None	No	17	Tx failure	BL & 9d tx	No
27	Non-cooperation	BL & 5d tx	No	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	No
97	tx failure & adverse r	Baseline	Yes	121	Non-cooperation	BL & 9d tx	No
106	Tx failure	None	No	127	Non-cooperation	BL	No
113	Adverse rxn	None	Yes	128	?	None	No
114	?	None	No	140	Diary card missing	None	No
132	Diary card missing	None		141	Diary card missing	None	No
139	Non-cooperation	None		145	Left trial area 2d	BL & 7d tx	No
143	Non-cooperation	BL & 9d tx					

**Reviewer Comment:** *Not acceptable. The sponsor provided raw data for 122 subjects. Patients excluded by the sponsor from the raw dataset for efficacy or safety analysis are indicated in the tables of withdrawals and protocol deviations below. It is not acceptable, for example, for the sponsor to exclude patient 106 because of "treatment failure." The sponsor should provide all raw data to be available for intent-to-treat and per protocol analysis. For the purpose of this review, however, all raw data provided for the 122 subjects was analyzed using both a per-protocol observed cases and modified intent-to-treat last-observation-carried-forward method.*

**Demographics:**

Subjects		Nedocromil	Placebo	All Patients	Percent
Total number of pts		64	62	126	
Gender	Female	39	35	74	59%
	Male	24	27	51	40%
	Not recorded	1	0	1	
Mean Age (Years)		22.4	21.4	21.9	
Age Range		7 to 60	8 to 51	7 to 60	

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

**Study Flow Chart**

Medication		2% Nedocromil Sodium Eye Drops in Placebo Eye Drops						
Phase	Recruitment Phase	Pre Pollen Challenge		Pollen Challenge				
Weeks		0	1	2	3	4	5	6
Visits	1	2	3	4				5

**Subject Population:** Patients had a history of seasonal allergic conjunctivitis, and met the inclusion and exclusion criteria.

**Inclusion Criteria**

- Males or females, aged 7 years or over, who were able to comply with test procedures.
- Patients with seasonal allergic conjunctivitis to birch pollen diagnosed on symptoms such as itching, soreness, photophobia, redness, blepharospasm, grittiness and watery discharge.
- Patients known to have had seasonal allergic conjunctivitis to birch pollen for the past two seasons.
- Patients with a positive skin test to birch pollen.
- Patients with concomitant rhinitis or asthma were included
- Patients had to remain in their locality for the duration of the study.
- Patients, or guardians, had to give written informed consent to the study.

**Exclusion Criteria**

- Patients with any additional eye disease which might have interfered with the study.
- Patients who would have worn contact lenses during the course of the study.
- Patients who needed to take systemic topical corticosteroids, systemic antihistamines or topical sodium cromoglycate.
- Patients who had received hyposensitisation treatment during the last 12 months.
- Patients who had received hyposensitisation treatment during the last 12 months.
- Patients who were pregnant or who were likely to become pregnant during the study.

**Reviewer Comment:** *Acceptable.*

**Criteria for evaluation:****Efficacy:**

Patient's opinions: Same as study CR1156.

Additionally, patients were to respond "yes" or "no" to the question: "Were the eye drops acceptable and well tolerated as a form of treatment?"

**Investigator's opinion:** Same as study CR1156.

**Diary Card Assessments and Diary Card Variables: Same as study CR1156**

**Clinical Assessments:**

At each visit, the investigator evaluated the following eye symptoms on a 0-4 scale as detailed below:

- 0=None
- 1=Mild
- 2=Moderate
- 3=Severe
- 4=Very Severe

Overall eye condition  
Itching of Eyes  
Soreness of eyes  
Grittiness of eyes  
Photophobia  
Blepharospasm  
Watery discharge of eye

**Primary Variables**

Diary card assessments  
Usage of concomitant eye medication  
Patient's opinion  
Clinician's opinion

**Secondary Variables**

Acceptability  
Clinical assessment

**Safety :**

At each visit the investigator discussed with the patient any complaints which might have been adverse drug reactions. Any complaint which the investigator regarded as "possible" or "probable" reactions to the trial treatment were to entered on the assessment form. These records were used to assess the incidence of adverse reactions.

**Reviewer Comment:** *Investigator interpretation and triage of adverse events prior to entry on assessment form may result in under-reporting of adverse events.*

**Withdrawals and Exclusions:**

Patients were allowed to withdraw from the study for any reason. The reasons were categorized and recorded according to the following list.

- Non-cooperation
- Severe concurrent illness
- Treatment failure
- Adverse reaction
- Removal outside trial area
- Other

Table of individual patients not completing the study:

Pt No	Days of Tx	Reason	Treatment	Clinic	Sponsor Excluded Analysis	Medical Officer Per Protocol Observed Cases	Medical Officer ITT LOCF
128	0	Withdrew Consent	Placebo	Kuopio	Efficacy Safety	Excluded	Excluded—No Data
21	6	Non-cooperation	Nedocromil	Kuopio	Efficacy Safety	Excluded	Excluded—No Data
27	25	Non-cooperation	Nedocromil	Vantaa, Helsinki		Excluded	Included
97	14	Treatment failure and adverse reaction	Nedocromil	Vantaa, Helsinki		Excluded	Included
106	14	Treatment failure	Nedocromil	Vantaa, Helsinki	Efficacy Safety	Excluded	Excluded—No Data
113	4	Adverse reaction	Nedocromil	Vantaa, Helsinki		Excluded	Included—blank data
139	-	Treatment failure and non-cooperation	Nedocromil	Oulu		Excluded	Included—blank data
143	14	Non-cooperation	Nedocromil	Oulu		Excluded	Included—blank data
17	18	Treatment failure	Placebo	Kuopio		Excluded	Included
77	15	Treatment failure	Placebo	Korvala, Helsinki		Excluded	Included
94	28	Severe concurrent illness	Placebo	Vantaa, Helsinki	Efficacy Safety	Excluded	Excluded—No Data
96	28	Severe concurrent illness and treatment failure	Placebo	Vantaa, Helsinki		Excluded	Included
107	28	Treatment failure and removal outside of area	Placebo	Vantaa, Helsinki		Excluded	Included
111	28	Severe concurrent illness	Placebo	Vantaa, Helsinki		Excluded	Included
112	28	Non-cooperation and treatment failure	Placebo	Vantaa, Helsinki		Excluded	Included
121	14	Non-cooperation	Placebo	Oulu		Excluded	Included
127	2	Non-cooperation	Placebo	Oulu		Excluded	Included
140	-	Non-cooperation	Placebo	Oulu		Excluded	Included—blank data
141	-	Treatment failure and non-cooperation	Placebo	Oulu		Excluded	Included—blank data
145	13	Other and removal outside of area	Placebo	Oulu		Excluded	Included

One patient (Number 128 vehicle) was excluded from the analysis after he withdrew consent to participate in the study. Nineteen patients did not complete the six-week treatment period.

### Protocol Violations

There were two systematic deviations from the protocol in this study.

1. Clinical Trials supplies arrived late at some investigator centers, therefore all of the patients entered the study during the pollen challenge instead of two weeks prior to the onset of the pollen season.
2. Two centers Dr Koivunen (Kanvala), Dr Takalo (Oulu) shortened the length of treatment period by two weeks to four weeks, with clinical assessments after two and four weeks.

**Table of Individual Patient Protocol Deviations**

Pt No	Days of Tx	Reason	Treatment	Medical Officer Per Protocol Observed Cases	Medical Officer ITT LOCF
1		Did not use medication as directed	Nedocromil	Exclude	Include
4		Did not complete treatment - Lost bottle; Left trial area	Nedocromil	Exclude	Include
27	12	Lost diary card	Nedocromil	Exclude	Include-Partial data
38	8	Lost diary card	Nedocromil	Exclude	Include-Partial data
76		No record of taking test treatment on second card	Nedocromil	Exclude	Include
85		Fever - stayed indoors	Nedocromil	Exclude	Include-Partial data
97		Withdrew before return to clinic Wore contact lenses	Nedocromil	Exclude	Include-Partial data
124		Use of sodium cromoglycate on first study day	Nedocromil	Exclude	Include
132		First diary card missing	Nedocromil	Exclude	Include but blank data
133		No final assessment	Nedocromil	Include	Include
139		No diary cards and other medications	Nedocromil	Exclude	Include but blank data
10	8	Left trial area	Placebo	Exclude	Include
17		Late assessment visit	Placebo	Include	Include
43	8	Lost diary card	Placebo	Exclude	Include-Partial data
47	15	Left trial area	Placebo	Exclude	Include-Partial data
67		Gastroenteritis - stayed indoors	Placebo	Exclude	Include-Partial data
121		Late assessment visit	Placebo	Include	Include
125		Forgot to complete diary card	Placebo	Exclude	Include
127		Test treatment recorded 2 Days - No last visit	Placebo	Exclude	Include
140		No diary cards/No final assessment	Placebo	Exclude	Include but blank data
141		No diary cards/No final assessment	Placebo	Exclude	Include but
145		Left trial area 2 days	Placebo	Exclude	Include-Partial data
148		Left trial area 1-day	Placebo	Exclude	Include

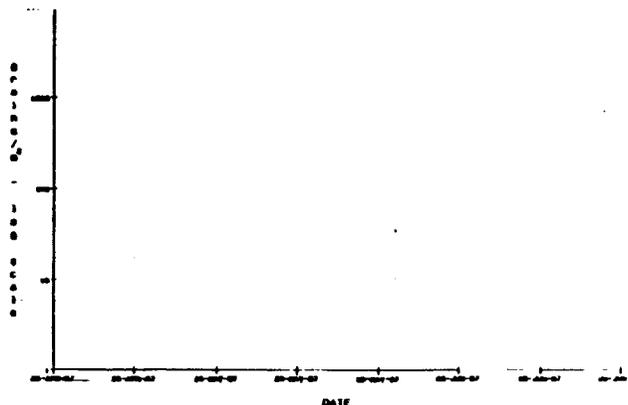
**Reviewer Comment:** *The type of analysis from which the protocol deviation patients were excluded is indicated in the table above.*

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OF ORIGINAL

## Birch Pollen Count Kuopio 1987

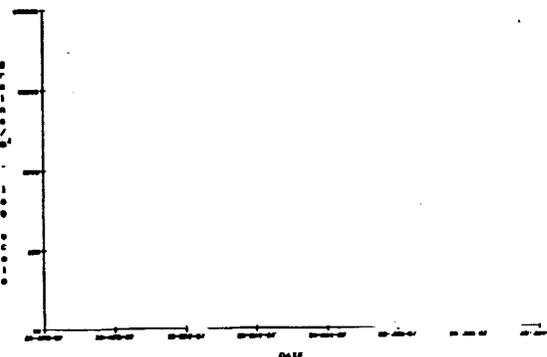
**Reviewer Comment:** *Not acceptable. The raw pollen count data are not provided. However, the graphic representation of the peak pollen period is clearly legible. Reproductions of the sponsor's graphic representation are provided at right for each center.*

*In Kuopio the peak pollen count drops below 100 grains/m<sup>3</sup> on May 25, May 26, and May 28. According to the graphic representation, the pollen count never drops below 50 grains/m<sup>3</sup>.*



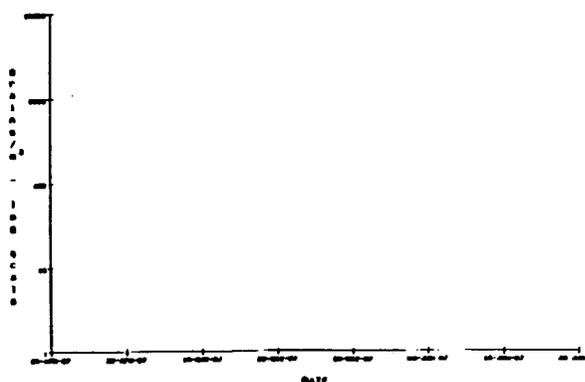
## Birch Pollen Count Helsinki 1987

**Reviewer Comment:** *In Helsinki, the pollen count is well above 100 grains/m<sup>3</sup> on all days of the designated peak pollen period of May 14, 1987 to May 28, 1987.*



## Birch Pollen Count Data Oulu, 1987

**Reviewer Comment:** *In Oulu, the pollen count is above 100 grains/m<sup>3</sup> on May 16 through May 19, 1987. The pollen count drops below 50 grains/m<sup>3</sup> from May 20 through May 26, 1987. The Pollen count increases to above 100 grains/m<sup>3</sup> on May 28.*



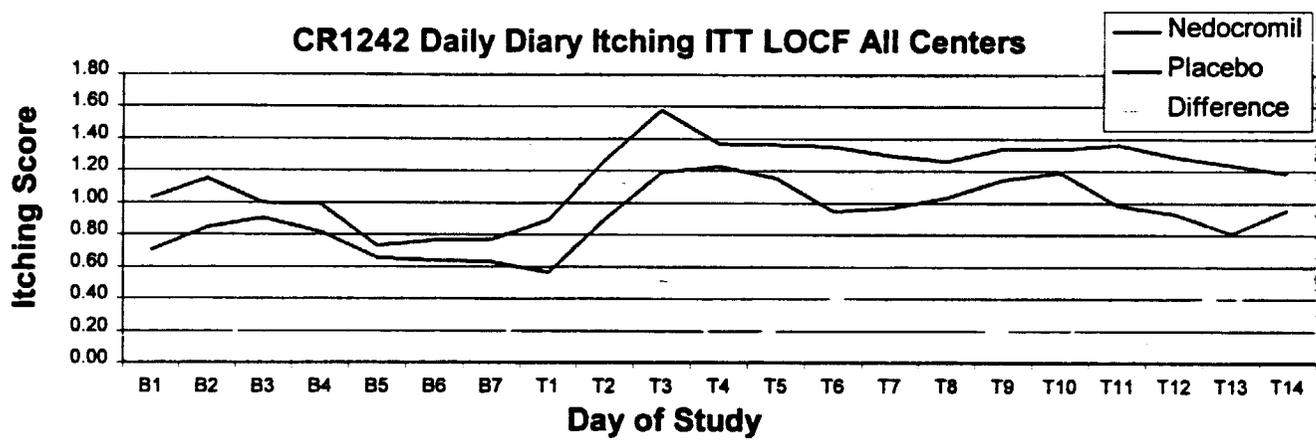
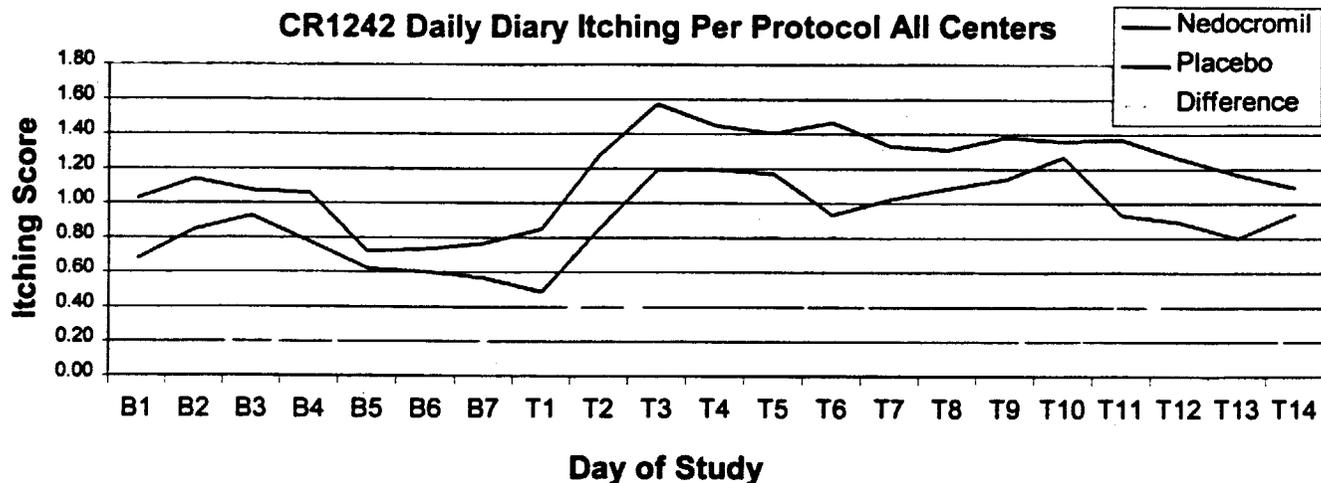
**Reviewer Comment:** *The peak pollen count is recorded to profile a pollen season. It is not representative of an individual patient's experience. Therefore, it is not acceptable to exclude some data by dividing the peak pollen period. For the purposes of this review, the peak pollen period is defined as a two-week period starting with a rise in the peak pollen count to above 100 grains/m<sup>3</sup> (See table below). The baseline period is defined as the seven day period preceding the peak pollen period.*

Location	Sponsor Peak Pollen Period 1	Sponsor Peak Pollen Period 2	Mean Pollen Count	Start Tx	Minimum # Days before Peak Pollen Period	# of Patients	Medical Officer Peak Pollen Period	Medical Officer Baseline Period
Kuopio	May 15 to May 24	May 30 to June 4	946	4-May	9	30	May 13 to May 26	May 6 to May 12
Mulken, Helsinki	May 14 to May 28		4302	May 8 to May 15	0 to 7	14	May 14 to May 27	May 7 to May 13
Konvala, Helsinki	May 14 to May 28		4302	1-May	14	22	May 14 to May 27	May 7 to May 13
Vantaa, Helsinki	May 14 to May 28		4302	28-Apr	16	27	May 14 to May 27	May 7 to May 13
Oulu	May 16 to May 19	May 29 to June 7	1330	May 11 to May 14	2 to 5	30	May 16 to May 30	May 9 to May 15

**Reviewer Comment:** *The sponsor asserts that study 1242 should not be included in the efficacy analysis because study drug supplies were delivered late. Thus, the study was not able to demonstrate a prevention of symptoms because subjects were not allowed preliminary mast-cell stabilization for the two weeks baseline period prior to peak pollen period challenge.*

*To evaluate these claims, the time of starting study drug was recorded as a range for each center. The first date in the range is the earliest date that at least half of the study subjects received the study drug. The second date in the range is the earliest date three-quarters of the study subjects received the study drug. If three-quarters of the study subjects received the drug at the start of the study then only one date was recorded. The minimum number of days prior to peak pollen period challenge was then recorded for both groups. For centers Konvala and Vantaa, (47 patients) greater than three-quarters of the subjects received the study drug for at least 14 days prior to peak pollen period challenge. The remaining three centers (74 patients) had from 0 to 9 days before three-quarters of the patients received the study drug. All study subjects received the study drug by the start of the peak pollen period. Kuopio, Konvala, Vantaa, and at least half the patients at Mulken received the study drug during the entire baseline. Thus, although the study may not be valid to evaluate prevention, it still offers data comparable to the other studies regarding efficacy. This reviewer does not accept that the study should be completely disregarded.*

*For the purpose of this review, the data was analyzed by comparing the two groups for equivalency for a Medical-Officer-defined seven day baseline period prior to the peak pollen period. The two groups were then compared for efficacy for the fourteen-day Medical Officer-defined peak pollen period. (See table above)*

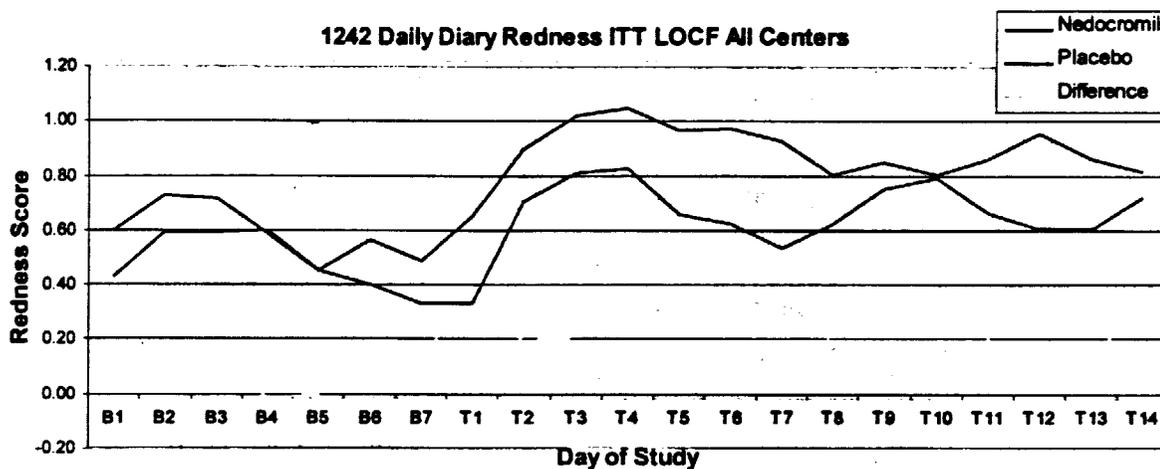
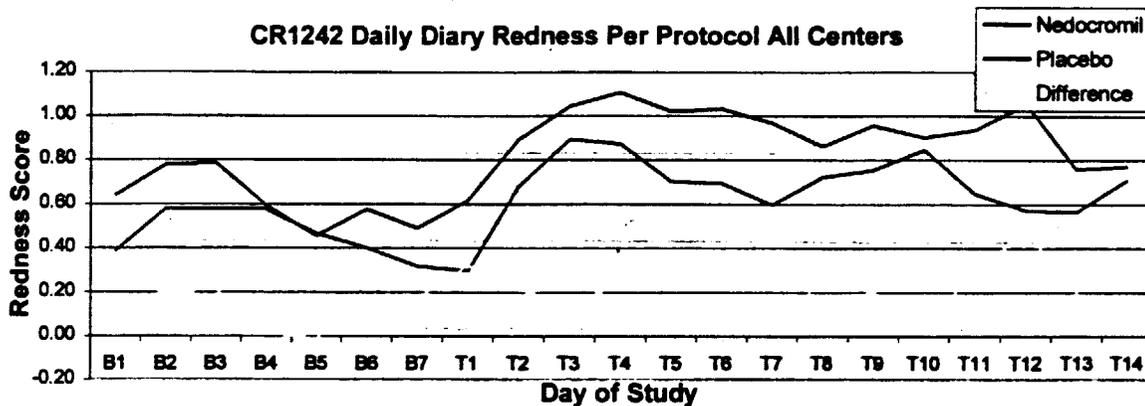


**Statistical Analysis of 1242 Itching**

Itching Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust	Difference
Placebo	0.89	46	1.32	47	0.45				
Nedocromil	0.73	46	0.99	47	0.26	Not done	0.067	0.008	0.33
Itching ITT									
Placebo	0.87	55	1.33	56	0.47				
Nedocromil	0.74	56	1.01	57	0.29	Not done	0.21	0.007	0.32

**Reviewer Comment:** Study 1242 shows a graphic trend toward reducing the itching associated with allergic conjunctivitis. This is statistically significant.

APPROVED THIS WAY  
BY CRIMINAL



**Table of Statistical Analysis of CR1242 Redness:**

Redness Per Protocol	Baseline	# Pts	Peak Period	# Pts	Difference	Koch's	Adjust Baseline	Not Adjust Baseline	Difference
Placebo	0.58	46	0.93	47	0.38				
Nedocromil	0.48	46	0.68	47	0.23	Not done	0.078	0.038	0.25
<b>Redness ITT</b>									
Placebo	0.54	55	0.9	56	0.36				
Nedocromil	0.48	56	0.67	57	0.21	Not done	0.019	0.026	0.23

**Reviewer Comment:** *A trend toward efficacy in reducing redness reaches statistical significance only when the baseline is adjusted in the ITT LOCF group.*

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**Adverse Events:****Table of Unusual Symptoms:**

Experience	Nedocromil	% Nedocromil n = 64	Placebo	% Placebo n = 62
Stinging	4	0%	4	6%
Burning	2	3%	0	0%
Soreness	2	3%	0	0%
Itching	0	0%	3	5%
Grittiness	1	2%	0	0%
Photophobia	1	2%	0	0%
Eczema of Eye Lids	0	0%	1	2%
Strange Taste	1	2%	0	0%
Rhinitis	0	0%	1	2%
Wheezy	0	0%	1	2%
Blurred Vision	0	0%	1	2%
Not Stated	0	0%	1	2%

**Reviewer Comment:** Adverse events will be included in the label as appropriate.

APPEARS THIS WAY  
ON ORIGINAL

**7.1.10 Study #10 Protocol #CR1901****Title: A Multicenter Double-Blind Group Comparative Study of 2% Nedocromil Sodium Eye Drops With 2% sodium cromoglycate and Placebo Eye Drops in the Treatment of Allergic Conjunctivitis to birch pollen.**

**Objectives:** To compare the efficacy and tolerability of 2% nedocromil sodium administered twice daily and vehicle administered twice daily, with cromoglycate and vehicle administered four times daily in the control of symptoms of birch pollen provoked allergic conjunctivitis.

**Study design:** The trial was designed as a multi-center, double-blind, double-dummy, group comparative study where patients with a pre-history of allergic conjunctivitis to birch pollen entered the study just before the birch pollen season began. Following a pre-trial visit between one and two weeks prior to the start of the treatment period, patients were randomly allocated to receive one of the following for a period of 4 weeks:

- Nedocromil sodium eye drops bid + vehicle eye drops bid.
- Sodium cromoglycate eye drops qid
- Vehicle eye drops qid

**Drug Schedule:**

- Dosing of Nedocromil was one drop in both eyes delivered twice daily for 4 weeks plus vehicle one drop in both eyes delivered twice daily for 4 weeks.
- Dosing of Chromoglycate was one drop in both eyes delivered four times daily for 4 weeks.
- Dosing of Vehicle was one drop in both eyes delivered four times daily for 4 weeks.

**Table of Investigators:**

Investigator	City, Country	# Randomized
E. Takalo	Oulu, Finland	23
R. Suves	Pori, Finland	21
P. Nordgren	Torju, Finland	33
A.L. Latvala	tampere, Finland	29
Dr M Leino	Kuopio, Finland	53
Dr K Ennevaara	Kajaani, Finland	14
A.M. Posti	Joensuu, Finland	22

**Study Plan:** The trial was designed as a multi-center, double-blind, double dummy, group comparative study where patients with a pre-history of allergic conjunctivitis to birch pollen entered the trial just before the birch pollen season began. Following a pre-trial visit between one and two weeks prior to the start of the treatment period, patients were randomly allocated to receive one of the following treatments for a period of four weeks:

The nedocromil sterile aqueous isotonic eye drops contained the following:

Nedocromil sodium	2.00%
Benzalkonium chloride (BKC)	0.01%
Edetate disodium (EDTA)	0.05%
Purified water to 100%	

APPEARS THIS WAY  
ON ORIGINAL

The cromoglycate sterile aqueous isotonic eye drops contained the following:

Cromoglycate sodium	2.00%
Benzalkonium chloride (BKC)	0.01%
Edetate disodium (EDTA)	0.05%
Purified water to 100%	

The matching vehicle solution contained riboflavin colorant in a 10 mL plastic dropper bottle.

**Concomitant Medication:** Artificial tear solution, polyvinyl alcohol, was supplied by the sponsor company to be used on a PRN basis when prescribed by the investigator. All medications being used for the treatment of eye symptoms at the time of entry into the trial were to be discontinued for the duration of the study. Topical nasal medication for allergic rhinitis including sodium cromoglycate, beclomethasone dipropionate and flunisolide were allowed to control nasal symptoms. It was required that all usage be recorded in the patient's diary booklet.

**Number of subjects (planned and analyzed):** Approximately 195 subjects entered, 185 were randomized.

### Study Flow Chart

Week	Pre-Seasonal Assessment		Treatment Phase				
	-2	-1	0	1	2	3	4
Visit	1		2	3			4
Lab Tests	1						2

**Subject Population:** Patients had a history of seasonal allergy to birch pollen, and met the inclusion and exclusion criteria.

### Inclusion Criteria

- Healthy male, or healthy female between the ages of 12 and 65, inclusive.
- A positive skin test to birch pollen.
- No history of being symptomatic to other allergens which affect the eye between 1<sup>st</sup> May and 15 June and who had been treated for moderate to severe allergic conjunctivitis to birch pollen for at least two previous seasons during which time their immunotherapy had not been altered.
- 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 or rhinitis on physical exam.

### Exclusion Criteria

- Patients with any additional eye disorder that may have interfered with the study.
- Patients who wore or intended to wear contact lenses during the treatment period.
- Patients who had significant renal, hepatic, cardiovascular or hematopoietic diseases.
- Patients using systemic or ophthalmic topical corticosteroids, antihistamines or ophthalmic sodium cromoglycate, from one week before Visit 2 and throughout the treatment period.
- Patients who were undergoing routine immunotherapy for the first time.
- Patients who had undergone routine immunotherapy and had not demonstrated allergic conjunctivitis in a subsequent season.
- Patients who required systemic corticosteroids and/or any systemic antihistamines.
- Patients who required any other medication with antihistaminic effects (e.g. H2 antagonists, psychotropic agents).
- Patients who were pregnant or nursing, at risk of pregnancy or not following adequate contraceptive techniques.

**Reviewer Comment:** *Acceptable.*

**Criteria for evaluation:**

**Efficacy:**

**Primary Outcome Variables**

- Diary card scores of the following eye symptoms: itching, redness, watery discharge, soreness/grittiness and photophobia. The patient recorded the severity of each eye symptoms on the following scale:

- 0 = No symptoms
- 1 = Mild symptoms (just noticeable)
- 2 = Moderate symptoms (noticeable but tolerable)
- 3 = Severe symptoms (severe enough to interfere with daily activities)
- 4 = Very severe symptoms (intolerable, all daily activities disrupted)

The patient also recorded the speed of effect of the test eye drops administered at 20.00 hours in hours and/or minutes.

At Visit 4, the patient gave his/her opinion of the test treatment on the following scale:

- 0 = No control of symptoms
- 1 = Slight control of symptoms
- 2 = Moderate control of symptoms
- 3 = Full control of symptoms

At the final visit the patient also gave his/her opinion of the acceptability and tolerability of the test treatment.

- The speed of effect of the test medication recorded during the peak pollen period.
- The patient's overall opinion of the treatment.

**Secondary Variables**

- All other variables measured during the study were considered to be secondary variables.

**Assessment by the Investigator**

The patient's current eye symptoms were assessed at each visit, on the following scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = severe
- 4 = Very Severe

After a total of 4 weeks' treatment a final assessment was made and the investigators opinion of treatment efficacy was recorded on the following scale:

- 0 = No control of symptoms
- 1 = Slight control of symptoms
- 2 = Moderate control of symptoms
- 3 = Full control of symptoms

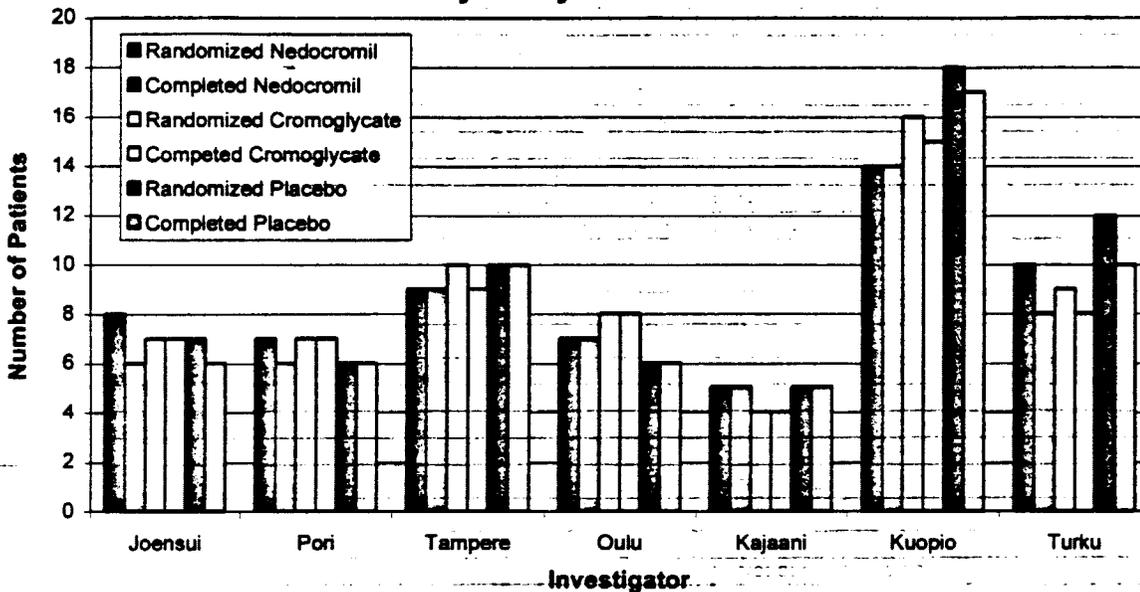
**Safety Variables:**

- The investigator inquired about, assessed and recorded any unusual symptoms.
- Adverse reactions were recorded and reported to Fisons.
- Blood and urine samples were taken at Visits 1 and 4 for examination of full blood count, differential white cell count, platelets, electrolytes, total protein, creatinine, alkaline phosphatase, SGOT, SGPT, glucose, urine blood, sugar, and protein.

Daily birch pollen counts were provided by the Finnish Pollen Bureau.

**Disposition:**

**Study 1901 Patient Disposition  
by Study Center**



**Withdrawals and Exclusions:** The patient may withdraw consent for personal reasons at any time.

**Clinical Assessment**

Protocol Violation	Nedocromil	Cromoglycate	Placebo	Total
Returned late for clinical assessment	14	14	17	25

Forty-five patients returned late for clinical assessment and in most cases more than two days after the last recording of test medication on their diary cards. Data relating to assessment of eye symptoms recorded at these visits were excluded from the analysis.

**Diary Card Data**

Protocol Violation	Nedocromil	Cromoglycate	Placebo	Total
Moved outside study area or concurrent illness confined to house	5	2	0	7
Took prohibited medications during study	10	9	0	25
Used only drops from one bottle	1		1	2
No laboratory data supplied	0	Pt 189, 224, 237, 243	Pt 238	5
Blood and urine samples for Visit 1 taken during treatment period, or samples for Visit 4 (end of study) taken more than 2 days after treatment stopped	19	18	23	40

**Table of Patient Withdrawals and Exclusions**

Ten patients withdrew from the study without taking test treatment and were excluded from the analysis. Twelve patients withdrew from the study without completing the four-week treatment period.

Reason for Withdrawal	Nedocromil	Cromoglycate	Placebo	Total
Suspected adverse reaction	2	1	0	3
Treatment failure	2	1	1	0
Suspected adverse reaction and treatment failure	1	0	0	1
Non cooperation	0	1	2	3
Other	0	0	1	1
Total Withdrawals	5	3	3	8

**Pollen Count:** Birch pollen counts were recorded daily in Kuopio, Oulu and Ruku between 12 April and 13 June 1989.

Study Center	Peak Pollen Period	Mean Pollen Count	Range
Kuopio	May 2, 1989 to May 13 1989	1207.5	315 to 3850
Oulu	May 13, 1989 to May 28 1989	2246.1	332 to 8631
Turku	April 26, 1989 to May 13, 1989	820.4	6 to 6321

The pollen counts from Kuopio were used in the analysis of data from Kuopio and Joensuu. Counts from Oulu were used for analysis of data from Kajaani and counts from Turku were also used to analyze data from Pori and Tampere.

**Reviewer Comment:** *Not Acceptable. Data on patient race and iris color were not provided.*

**Efficacy:** Mean scores during the peak pollen period were calculated for each symptom for each patient. These scores were analyzed center by center and for all centers combined. For all centers combined, a significant difference between treatments was seen for itching. When pairwise comparisons of the mean values were made using Mann-Whitney U-tests, patients in the nedocromil sodium and sodium cromoglycate groups had significantly less itching than those in the vehicle group. No significant difference was seen between the two active treatments. No significant difference between treatments were seen for the remaining variables in the combined analysis.

### Analysis of Patient-Reported Symptoms on Diary Card Data – All Centers

	Mean	Sample Size
<b>Itching</b>		
Nedocromil Sodium	1.14	52
Sodium Cromoglycate	1.05	56
Placebo	1.37	56
Kruskal-Wallis Statistic (df)	6.27	2
P Value	0.044	
<b>Redness</b>		
Nedocromil Sodium	0.86	52
Sodium Cromoglycate	0.76	56
Placebo	0.87	56
Kruskal-Wallis Statistic (df)	0.57	2
P Value	0.75	

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### Summary of Pairwise Comparisons for Patient Diary Card Data: Itching

	Nedocromil Sodium	Sodium cromoglycate	Placebo
Symptom score (n)	1.14 (52)	1.05 (56)	1.37 (56)

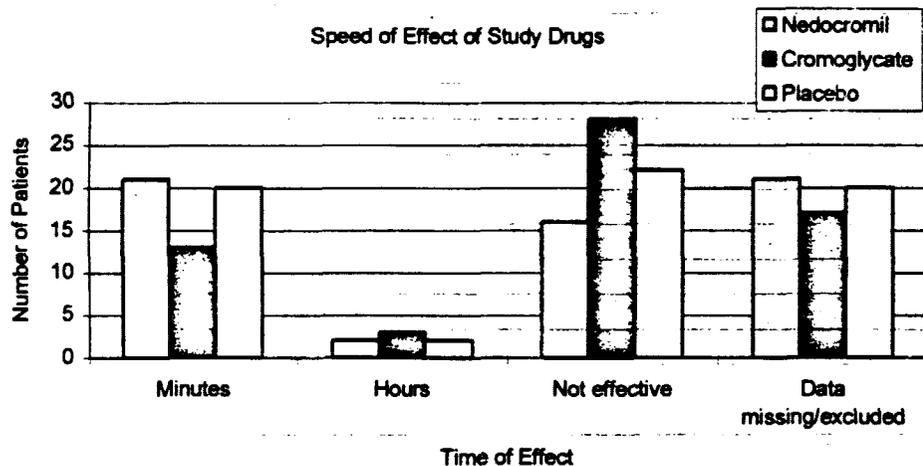
	Mann-Whitney U-Value	P-Value	Mack-Skillings Statistic	P-Value
Nedocromil Sodium vs Placebo	1176.5	0.086	2.35	0.03
Sodium Cromoglycate vs Placebo	1154.5	0.016	6.68	0.0002
Nedocromil Sodium vs Sodium cromoglycate	1337.5	0.466	0.65	0.235

### Reviewer Comment:

*Data provided by the sponsor consisted only of summary statistics. This is not acceptable. Mean symptom data was provided only over the entire peak pollen period. No daily means were provided. Relying on the sponsor statistical analysis, patient daily diary data comparing Nedocromil with Vehicle showed statistical significance with the Mack-Skillings method, and did not show significance with the Mann-Whitney method. There was no statistical significance between groups in patient daily diary redness data. Study 1901 shows marginal efficacy for itching patient daily diary symptom score. A trend toward reduced itching does not reach statistical significance when both statistical methods are applied. Patients receiving cromoglycate show reduced itching which reaches statistical significance with both methods when compared with vehicle.*

	End of Baseline		Mean Change from Baseline			
	Week 0	N	Change	N (week 1)	Change	N (week 2)
<b>Itching</b>						
Nedocromil Sodium	1.2	51	-0.61	51	-0.61	39
Cromoglycate	1.04	52	-0.4	52	-0.59	41
Placebo	1.05	58	-0.3	56	-0.21	42
Kruskal-wallis Statistic (DF)	0.95	2	2.01	2	3.97	2
P Value	0.622		0.366		0.138	
<b>Hyperemia</b>						
Nedocromil Sodium	0.8	51	0.24	50	-0.24	38
Cromoglycate	0.85	52	-0.13	52	-0.15	41
Placebo	0.9	58	-0.2	56	0.1	41
Kruskal-wallis Statistic (DF)	0.75	2	0.59	2	2.2	2
P Value	0.687		0.745		0.333	

**Reviewer Comment:** *The investigator assessment of itching and redness failed to show statistically significant differences in efficacy between the Nedocromil, Cromoglycate, and Vehicle groups.*



**Reviewer Comment:**

*Many patients reported the study drug to be effective within minutes. The large number of missing and/or excluded data make this claim inconclusive, however. In addition, the speed of effect does not differ from vehicle.*

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**Adverse Events: Table of Unusual Symptoms:**

	Nedocromil	Sodium Cromoglycate	Placebo
Itching	4	3	3
Irritation	1	0	0
Grittiness	1	1	1
Soreness	9	3	4
Stinging	7	7	5
Smarting	1	0	0
Watering	2	1	0
Hyperemia	1	0	2
Discharge	0	0	1
Swollen Eye	1	0	0
Photophobia	1	1	0
Lid eczema	1	0	0
Dry Eyes	0-	1	0
Dry Under Lid	0	0	1
Pressure Under Lid	0	0	1
Taste	1	0	0
Itching Face	0	1	0
Eczema	0	1	0
Palmer Erythema	1	0	0
Stiffness	1	0	0
Dyspnea	1	0	0
Breathing Problems	0	1	0
Headache	1	0	1
Fever	0	1	0
Nausea	0	1	0

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## 8 Reviewer's Summary of Efficacy:

## Summary of Itching Efficacy

Study 1170/1	Mean score for itching					Koch's p-value (2-sided)	Mann-Whitney p-value		Difference PI - Ne Pk Period
	Tx	Baseline	# Pts	Peak Period	# Pts		Difference	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 1170/2									
Placebo	1.51	53	1.48	53	0.23				
Nedocromil	1.44	50	1.19	50	-0.14	0.33	0.176	0.028	0.29
Study 1343									
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
Study 1344									
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
Study 1959									
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
Study 1891 Per Protocol									
Placebo	1.03	80	1.2	78	0.21				
Nedocromil	1.1	79	1.12	77	0.02	Not done	0.013	0.354	0.08
S. Cromoglycate	1.02	80	1.19	80	0.16	Not done	0.112	0.49	0.01
Study 1891 ITT									
Placebo	1.07	90	1.29	88	0.24				
Nedocromil	1.12	89	1.13	87	0.007	Not done	0.003	0.195	0.16
S. Cromoglycate	1.04	89	1.22	89	0.188	Not done	0.142	0.434	0.07
Study 1871 Per Protocol									
Placebo	0.78	62	1.42	70	0.68				
Nedocromil	0.5	70	0.93	73	0.45	Not done	0.019	0.0008	0.49
Study 1871 ITT									
Placebo	0.77	64	1.44	72	0.69				
Nedocromil	0.52	73	1.01	76	0.51	Not done	0.04	0.005	0.43
Study 1242 Per Protocol									
Placebo	0.89	46	1.32	47	0.45				
Nedocromil	0.73	46	0.99	47	0.26	Not done	0.067	0.008	0.33
Study 1242 ITT									
Placebo	0.87	55	1.33	56	0.47				
Nedocromil	0.74	56	1.01	57	0.29	Not done	0.21	0.007	0.32
Study 1156 Per Protocol									
Placebo	1.28	35	1.23	34	-0.016				
Nedocromil	1.05	39	1.13	39	0.08	Not done	0.776	0.357	0.1
Study 1156 ITT									
Placebo	1.25	53	1.34	53	0.084				
Nedocromil	1.12	49	1.15	49	0.038	Not done	0.575	0.185	0.19

## Summary of Redness Efficacy

Study	Mean score for redness by investigator					Koch's p-value (2-sided)	Mann-Whitney p-value		Difference Pl - Ne Pk Period
	Baseline	# Pts	Peak Period	# Pts	Difference		Adjust baseline	Not adjust baseline	
Study 1170/1									
Placebo	1.05	42	1.29	42	0.23				
Nedocromil	1.14	43	1	43	-0.14	0.038	0.018	0.038	0.29
Study 1170/2									
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
Study 1343									
Placebo	1	63	1	63	0				
Nedocromil	1.05	58	1	58	-0.05	0.93	0.304	0.556	0
Study 1344									
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
Study 1959									
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
Study 1891 Per Protocol									
Placebo	0.94	80	1.08	78	0.15				
Nedocromil	0.85	79	0.91	77	0.06	Not done			0.17
S. Cromoglycate	0.79	80	0.97	80	0.18	Not done	0.095	0.167	0.11
Study 1891 ITT									
Placebo	0.91	90	1.16	88	0.21				
Nedocromil	0.88	89	0.95	87	0.06	Not done	0.03	0.197	0.21
S. Cromoglycate	0.78	89	0.96	89	0.19	Not done	0.359	0.23	0.2
Study 1871 Per Protocol									
Placebo	0.46	63	1.43	70	0.97				
Nedocromil	0.25	69	0.93	73	0.68	Not done	0.019	0.0005	0.5
Study 1871 ITT									
Placebo	0.47	65	1.44	72	0.98				
Nedocromil	0.25	72	1	77	0.74	Not done	0.037	0.003	0.44
Study 1242 Per Protocol									
Placebo	0.58	46	0.93	47	0.38				
Nedocromil	0.46	46	0.68	47	0.23	Not done	0.078	0.036	0.25
Study 1242 ITT									
Placebo	0.54	55	0.9	56	0.36				
Nedocromil	0.48	56	0.67	57	0.21	Not done	0.019	0.026	0.23
Study 1156 Per Protocol									
Placebo	0.95	35	1.02	34	0.1				
Nedocromil	0.75	39	0.89	39	0.15	Not done	0.7	0.262	0.13
Study 1156 ITT									
Placebo	0.93	53	1.1	53	0.16				
Nedocromil	0.78	49	0.86	49	0.08	Not done	0.443	0.096	0.24

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**Summary of Studies Reaching Statistical Significance:**

	Itching Adjust Baseline		Itching Not Adjust Baseline		Redness Adjust Baseline		Redness Not Adjust Baseline	
	PP	ITT	PP	ITT	PP	ITT	PP	ITT
Significant	4	3	4	4	3	4	2	2
Not Significant	6	7	6	6	7	6	8	8

*More weight is placed on the non-adjusted baseline data due to problems with reliable baselines identified in this and other reviews of this indication. If the assumption is made that data suppression by the sponsor did not occur, then a greater number of studies reached statistical significance showing efficacy of Nedocromil in reducing the itching associated with allergic conjunctivitis than would be expected by chance. This is not true of redness.*

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**9 Reviewer's Summary of Safety:**  
**Summary of Adverse Events:**

Event	Maximum	1170/2	1170/1	1343	1344	1959	1871	1156
Headache	54%	12%	5%	36%	54%	42%		2%
Nose stuffy	38%							38%
Nose running	30%			2%		1%	1%	30%
Nose congestion	28%							28%
Eye burning	21%	12%	19%	5%	13%	21%		14%
Taste perversion	21%	10%	21%	5%	13%	7%	3%	14%
Sneezing	18%					2%		18%
Pharyngitis	17%	6%		5%	17%	5%	1%	
Eye stinging	16%	2%	2%		10%	9%		16%
URI	14%			2%	14%	12%	1%	
Eye pain	14%						14%	
Asthma	10%						4%	10%
Rhinitis	10%			2%			1%	10%
Eye irritation	7%		7%					
Nose itching	6%							6%
Tonsillitis	6%							6%
Eye itching	5%		2%		1%	1%	5%	
Eye grittiness	5%	2%	5%			2%		
Eye redness	5%	2%	5%					
Photophobia	5%	2%	5%					
Neuralgia	5%		5%			1%		
Nose burning	5%		5%					
Infection, Viral	4%			3%	4%			
Bronchospasm	4%	4%		2%		2%		
Coughing	4%	2%		2%		4%	3%	
Diarrhea	4%	4%		2%	1%			
Dysmenorrhea	4%			3%	1%	4%		2%
Eye soreness	4%	2%					1%	4%
Myalgia	4%	4%		2%	3%	1%		
Epistaxis	3%			2%	3%			
Arthralgia	3%			3%	1%	3%		
Conjunctivitis	3%			2%	3%	1%		
Dyspepsia	2%		2%		1%	2%		
Earache	2%		2%		1%	2%	2%	
Blindness -night	2%		2%					
Eye dryness	2%	2%	2%					
Migraine	2%		2%	2%				
Nose soreness	2%		2%					
Dyspnea	2%			2%		1%		
Fever	2%	2%		2%		1%		
Nausea	2%	2%		2%	1%	1%		
Pain	2%			2%	1%	1%		
Abdominal Pain	2%			2%				
Arthritis	2%			2%				

Back Pain	2%			2%		2%		
Bee sting	2%			2%				
Chest Pain	2%			2%				
Corneal opacity	2%			2%				
Corneal ulceration	2%		2%					
Eye watering	2%			2%				2%
Eye puffy	2%							2%
Face edema	2%							2%
Glaucoma	2%			2%				
Herpes simplex	2%			2%				
Malaise	2%		2%					
Menstrual Disorder	2%			2%				
Mouth itchy	2%							2%
Post nasal drip	2%		2%					
Rash	2%					2%		
Tendinitis	2%			2%				
Tooth Disorder	2%			2%				
Vomiting	2%		2%					
Pneumonia	1%					1%		
Abscess	1%				1%			
Acne	1%					1%		
Allergic Reaction	1%					1%		
Allergies	1%				1%			1%
Application site reaction	1%				1%			
Constipation	1%					1%		
Dermatitis	1%				1%			
Dizziness	1%				1%			
Flatulence	1%				1%			
Fluid Retention	1%					1%		
Gastroenteritis	1%					1%		
Hypertonia	1%					1%		
Hypesthesia	1%					1%		
Influenza-like Sx	1%					1%		
Insomnia	1%				1%			
Laryngitis	1%					1%		
Micturition frequency	1%				1%			
Nail disorder	1%				1%			
Otitis Media	1%					1%		
Pruritus	1%				1%			
Renal calculus	1%					1%		
Retinal detachment	1%				1%			
Sinusitis	1%				1%	1%		
Sputum Increased	1%					1%		
Synovitis	1%				1%			
Twitching	1%					1%		
Urticaria	1%				1%			
UTI	1%					1%		
Vision abnormal	1%				1%	1%		

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LABELING

**Conclusions:**

1. More studies reach statistical significance regarding the efficacy of Nedocromil to treat the itching associated with allergic conjunctivitis than would be expected by chance.
2. In the studies where Nedocromil does not show statistical significance to treat itching, Nedocromil shows a trend toward treating itching over that seen by vehicle.
3. A similar pattern is not seen for redness. Nedocromil fails to show statistical significance in treating the redness associated with allergic conjunctivitis.
4. Data are missing or possibly suppressed in several studies. Case report forms are not available to verify that the sponsor has not suppressed data. The above conclusions are reached under the assumption that the sponsor did not manipulate or suppress data.
5. Nedocromil has been used for the treatment of allergic conjunctivitis in Europe and has been used extensively systemically. Nedocromil is a relatively safe treatment for the itching associated with allergic conjunctivitis.
6. Data was illegible in several places throughout the submission.
7. If available, the outcome information on the patient who received the drug product while pregnant should be submitted.

**Recommendations:**

1. NDA 21-009 does not provide sufficient information to support the indication of the treatment of allergic conjunctivitis because there is insufficient information to support the treatment of redness. The applicant should provide additional support or revise the indication.
2. NDA 21-009, nedocromil sodium ophthalmic solution is recommended for approval for the indication of the treatment of itching associated with allergic conjunctivitis contingent upon the applicant supplying case report forms that verify the submitted line listing.
3. The applicant should submit revised labeling, consistent with the recommendations listed in this review.

/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 LMC 10/1/99