

OPHTHALMIC DRUGS
SUBCOMMITTEE

JULY 21, 1999

CYCLOSPORINE NDA 21023

FDA BRIEFING PACKAGE

MEDICAL OFFICER'S REVIEW

Medical Officer's Review of NDA 21-023
Original

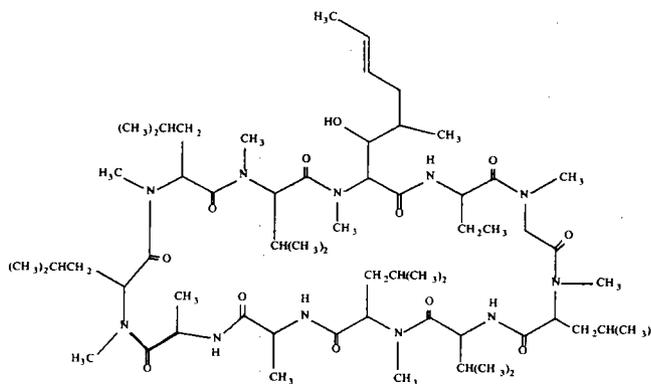
NDA 21-023
Medical Officer's Review Draft

Submission: 2/24/99
Review Completed: 5/17/99

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

Chemical Name: Cyclo[[*(E)*-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl]



Chemical Structure – Formula $C_{62}H_{111}N_{11}O_{12}$

Sponsor: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Pharmacologic Category: Immunomodulator

Proposed Indication: Treatment of moderate to severe keratoconjunctivitis sicca

Dosage Form and Route of Administration: Ophthalmic emulsion for topical ocular administration

NDA Drug Classification: 3 P

Related IND's:)

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3 Material reviewed
NDA 21-023 Volumes 1.1, 2.25-2.89

4 Chemistry/Manufacturing Controls –See Chemistry Review

Table 1
Quantitative Composition of Cyclosporine Ophthalmic Emulsion 0.05%

Ingredient	Concentration (% w/w)	Concentration (mg/g)	Amount for a batch
Cyclosporine USP	0.005	0.5	

Table 2
Product Tests, Specifications, and Analytical Methods for Cyclosporine Ophthalmic Emulsion 0.05%

Test	Release Specification
Cyclosporine	
Cyclosporine Identification	

5 **Animal Pharmacology/Toxicology** – No specific issues. See Pharmacology Review

6 **Clinical Background**

KCS, commonly referred to as dry eye, is a disease affecting the ocular surface, the tear film, and related ocular tissues and organs. The ocular surface is supported and maintained by the tear film, which is composed of 3 distinct components (lipid, aqueous, and mucin) that make up 2 fluid layers. Meibomian glands along the upper and lower lid margins produce the outer lipid layer of the tear film. The inner layer, an aqueous and mucin mixture, is composed of aqueous fluid produced by the main and accessory lacrimal glands and mucins produced by goblet cells on the conjunctival epithelium as well as corneal epithelial cells.

The dry-eye category characterized by aqueous deficiency can be further divided into patients with Sjögren's syndrome (a systemic autoimmune disease) and those with KCS in the absence of any related systemic disease (non-Sjögren's KCS).

The sponsor's present application considers an ophthalmic formulation of cyclosporine for the treatment of moderate to severe keratoconjunctivitis sicca. The active component of the formulation, cyclosporine, is expected to be beneficial to patients through its ability to modulate the immune reactivity and inflammatory processes.

6.1 Relevant Human Experience

Systemically administered SANDIMMUNE® was approved for use in organ transplantation in 1983. It was approved for use in rheumatoid arthritis and psoriasis in 1996. Alternate formulations have been studied, but not approved, for corneal graft transplantations.

6.3 Foreign Experience

Cyclosporine ophthalmic emulsion has not been marketed in any country nor has it been withdrawn from marketing in any country to date. There are no pending applications for cyclosporine ophthalmic emulsion in any foreign country.

6.4 Human Pharmacology, Pharmacokinetics, & Pharmacodynamics – See Pharmacology Review

7 Description of Clinical Data Sources

Table 3
Clinical Data Sources

Review Number	Protocol	Indication	Design	Treatment Arms	Number in Each Arm	Age Range (Years)	% (M/W) B/W/O	Duration of Treatment
1	002	Moderate to Severe Keratoconjunctivitis	Parallel Double-Masked	cyclo 0.05%	135	21 – 90 mean 59.3	(21/79) 5/77/18	6 months Treatment Phase
				cyclo 0.1%	134			6 months Extension Phase
				common vehicle	136			
				Pharmokinetic Levels	total 405			
2	003	Moderate to Severe Keratoconjunctivitis	Parallel Double-Masked	cyclo 0.05%	158	24 – 90 mean 59.8	(16/84) 4/91/5	6 months Treatment Phase
				cyclo 0.1%	158			6 months Extension Phase
				common vehicle	156			
					total 472			
3	001	Moderate to Severe Keratoconjunctivitis	Parallel Double-Masked	cyclo 0.05%	31	31 – 88 mean 58.6	(16/84) 7/90/3	12 weeks Treatment Phase
				cyclo 0.1%	32			
				cyclo 0.2%	34			
				cyclo 0.4%	32			
				vehicle of 0.2%	33			
	total 162							

8 **Clinical Studies**8.1.1 **Study #1 Protocol 192731-002**

Title: A Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study of the Safety and Efficacy of Cyclosporine 0.5% and 0.1% Ophthalmic Emulsions Used Twice Daily for Up to One Year in Patients with Moderate to Severe Keratoconjunctivitis Sicca

Objective: To evaluate the safety and efficacy of cyclosporine 0.05% and 0.1% ophthalmic emulsions compared with vehicle in patients with moderate to severe keratoconjunctivitis sicca (KCS).

Study Design: A randomized, multicenter, double-masked, vehicle-controlled, parallel-group study during the first six months. The second six-month period was a double masked extension phase in which all patients received one of the two concentrations of cyclosporine.

Test Drug Schedule: All subjects received either cyclosporine 0.05%, 0.1% or vehicle (identical to that used in both strengths) bilaterally, BID for 6 months. At the end of six months, cyclosporine groups continued their assigned masked treatment, and subjects in the vehicle group received masked 0.1% cyclosporine emulsion.

Principal Investigator	Investigator Number	No. of Patients Enrolled			Patient Numbers
		Vehicle	Cyclosporine		
			0.05%	0.1%	
	2697	10	10	10	209-229; 410-418
	2702	3	3	3	278-286
	0207	11	11	11	194-208; 314-328; 488-490

Principal Investigator	Investigator Number	No. of Patients Enrolled			Patient Numbers
		Vehicle	Cyclosporine		
			0.05%	0.1%	
	0595	2	2	2	101-106
	2705	5	5	4	152-163; 165-166
	0768	3	3	2	269-276
	2706	10	10	10	167-178; 329-340; 497-502
	1777	6	6	6	107-109; 179-193
	2707	30	30	30	110-136; 287-298; 341-355; 419-424; 428-430; 434-439; 464-475; 503-505; 512-514; 518-520
	2430	7	7	7	260-268; 371-379; 509-511

Principal Investigator	Investigator Number	No. of Patients Enrolled			Patient Numbers
		Vehicle	Cyclosporine		
			0.05%	0.1%	
	2366	18	17	18	380-400; 443-463; 476-486
	1783	17	17	17	137-151; 239-247; 299-313; 401-409; 440-442
	2708	10	10	10	251-259; 356-370; 491-496
	2709	4	4	4	230-238; 248-250

8.1.1 Study Design

Patients who met the protocol's inclusion/ exclusion criteria entered a Run-in Phase. During this phase,

Patients who completed the Run-in Phase and still qualified entered the Vehicle-Controlled Masked Treatment Phase. They were randomly allocated to receive either 0.05% or 0.1% cyclosporine or vehicle ophthalmic emulsion, to be given in each eye twice daily (BID) for 6 months. needed

At the end of 6 months, patients who completed the Vehicle-Controlled Masked Treatment Phase were eligible to enter the Cyclosporine Treatment Extension Phase. Patients who were in the 0.05% and 0.1% cyclosporine treatment groups continued their previously allocated masked treatment, while patients who were in the vehicle group received masked 0.1% cyclosporine ophthalmic emulsion. All patients were to use their masked study medication BID, _____, for an additional 6 months.

Subsets of patients at selected centers participated in pharmacokinetic testing. For the cyclosporine A trough concentrations, patients had blood samples drawn at the qualification visit and at _____ during the Vehicle-Controlled Masked Treatment Phase. Additional samples will be drawn at _____ for the cyclosporine A AUC evaluations, patients had blood samples collected at _____ after the morning dose during _____ of the Cyclosporine Treatment Extension Phase.

Study Medications:

- Cyclosporine 0.05% ophthalmic emulsion (Allergan formulation number 9054X), which contained 0.05% cyclosporine _____ Supplied in unit dose vials.
- Cyclosporine 0.1% ophthalmic emulsion (Allergan formulation number 8735X), which contained 0.10% cyclosporine _____ Supplied in unit dose vials.
- Vehicle of cyclosporine ophthalmic emulsion (Allergan formulation number 8922X) _____. This vehicle was identical to that used for both strengths of cyclosporine in this trial. Supplied in unit dose vials.
- REFRESH[®] (Allergan formulation number 7447X) _____

Supplied in unit dose vials.

Study Masking:

The study medication was packaged, labeled, and masked in a manner consistent with Good Manufacturing Practice (GMP) regulations for investigational supplies. Identical unit-dose vials were used to hold the study treatments, which were each of an identical milky color. The medication was identified as a new drug limited by federal law to investigational use only, and for external use only. The study number and patient number were printed on the unit label.

When necessary for the safety and proper treatment of the patient, the investigator could irreversibly unmask the tear-off portion of the patient's medication label to determine which treatment had been assigned, and institute appropriate follow-up care. When possible, the Sponsor was to be notified prior to unmasking the study medication. During the Vehicle-Controlled Masked Treatment Phase of the study, no patient's medication was unmasked.

Inclusion Criteria:

The following were requirements for entry at the screening visit:

- Male or female of legal age of consent
 - Signature on the Informed Consent Form and the Patient's Bill of Rights (if applicable)
 - Diagnosis of KCS with documented signs and symptoms (as listed below) despite conventional management, which may have included artificial tear drops, gels and ointments, sympathomimetic agents, and parasympathomimetic agents:
-
- Patient properly motivated and willing to cooperate with the investigator by following the required medication regimen; patient also willing and able to return for all visits during the study

- Female patient of childbearing potential used a reliable (to be determined by the investigator) form of contraception during the study; a female was considered to be of childbearing potential unless she was post-menopausal, without a uterus and/or both ovaries, or had bilateral tubal ligations
- A negative urine pregnancy test result in women of childbearing potential; a woman was considered to be of childbearing potential unless she was post-menopausal, without a uterus and/or both ovaries, or had bilateral tubal ligations
- Normal lid position and closure
- Best-corrected ETDRS visual acuity score of _____ (equivalent to a Snellen score of _____) in each eye
- The following topical (i.e., creams, ointments, or patches) or systemic medications were allowed as long as the patient had been on a stable dose for at least 90 days before the screening visit and through the 2-week Run-in Phase: estrogen-progesterone and other estrogen derivatives

The following were requirements for entry at the qualification visit:

- Diagnosis of KCS with documented signs and symptoms (as listed below) despite instructed management with REFRESH®:

Exclusion Criteria:

The following were criteria for exclusion at the screening and qualification visits:

- Any patient who had participated in the Sponsor's Phase 2 cyclosporine trial

- Any patient who had used topical or systemic cyclosporine within 90 days of the screening visit
- Concurrent involvement in any other clinical trial involving an investigational drug/device, or participation in a clinical trial within the last 30 days preceding the screening visit
- Female patient who was pregnant or nursing, or planning a pregnancy during the study
- Compromised cognitive ability that may have been expected to interfere with study compliance
- Uncontrolled systemic disease (e.g., hypertension, diabetes) or the presence of any significant illness (e.g., serious gastrointestinal, renal, hepatic, endocrine, pulmonary, cardiac, neurologic disease, cancer, AIDS, or cerebral dysfunction) that could have, in the judgment of the investigator, interfered with interpretation of the study results
- Required chronic use of topical ophthalmic or systemic medications (see list below) that have induced a dry-eye condition
- Patient used topical ophthalmic or systemic medications that may have affected a dry-eye condition less than 3 weeks before the screening visit, or during the Run-in Phase. These medications included general anesthetics, antihistamines (specifically azemizole [HISMANAL[®]] or loratadine [CLARITIN[®]]), cholinergic agents, antimuscarinics, beta-blocking agents, tricyclic antidepressants, phenothiazines, and topical ophthalmic steroids
- Patients who used any topical ocular medications without authorization from the Sponsor
- Known hypersensitivity to any components of the study or procedural medications
- KCS patients who had Schirmer readings _____ (without anesthesia) in _____ after nasal stimulation, _____
- Patients who responded "N/A" _____ or more on the OSDI[®] questionnaire
- Contact lens wear during the study
- Active ocular infection or non-KCS inflammation
- History of recurrent herpes keratitis or active disease within the last 6 months

Conjunctival Staining

Lissamine green was instilled, and interpalpebral conjunctival staining was evaluated only after 30 seconds, but before 2 minutes, had elapsed. Using white light of moderate intensity, the interpalpebral regions of the temporal and nasal conjunctiva were graded referring to the same Oxford Scheme. A negative change from baseline indicated improvement.

Sum of Corneal and Interpalpebral Conjunctival Staining

The sum of the temporal and nasal interpalpebral conjunctival staining was measured on an 11-point scale of severity (grades 0 to 10). The sum of corneal and interpalpebral (temporal and nasal) conjunctival staining was measured on a 16-point scale of severity (grades 0 to 15). A negative change from baseline indicated improvement.

Schirmer Tear Test

The Schirmer tear test was performed both with and without anesthesia. Sterile strips were inserted, and the tear front marked after 5 minutes (min). The amount of wetting was measured in millimeters (mm) using a graduated paper scale. Schirmer values were categorized from grade _____ . A positive change from baseline indicated improvement.

Tear Break-up Time

Time for tear break-up was measured only up to 10 seconds with a stopwatch. Three consecutive TBUT measurements were performed, and the actual times in seconds recorded if the first time was less than 10 seconds.

Subjective Symptoms

OSDI[®] Score (Ocular Surface Disease Index)

To evaluate their functional disability from dry eye, patients completed the OSDI[®] questionnaire.

_____ . A minimum entry score was required at the screening and qualification visits. A negative change from baseline indicated improvement.

Facial Expression Subjective Rating Scale

Patients chose one of the faces from the Facial Expression Subjective Rating Scale that reflected how their eyes felt over the previous week. The facial expressions ranged from 1 (happiest face) to 9 (unhappiest face). Responses were categorized from grade 1 (pictures 1 and 2) to grade 5 (pictures 8 and 9). A negative change from baseline indicated improvement.

Symptoms of Dry Eye

At the investigator's office, patients completed a questionnaire about symptoms of dry eye (ocular discomfort) in terms of stinging/burning, itching, sandiness/grittiness, blurred vision, dryness, light sensitivity, painful or sore eye, and other. Symptoms were graded

using a scale of 0 (do not have this symptom) to +4 (always notice this symptom). A negative change from baseline indicated improvement.

Investigator's Global Evaluation of Response to Treatment

The investigator completed a global evaluation of the overall effect of study medication relative to the qualification visit. _____

Treatment Success

Treatment success was defined as a global response of approximately _____ or better _____

Other Variables

Date and time of last use of REFRESH[®] prior to each follow-up examination were documented on the case report forms (CRFs). Average number of times per day the patient needed to use REFRESH[®] during the previous week and number of days patient was able to go without using any REFRESH[®] during the previous week were recorded.

_____ meibomian glands were selected, and the number of glands from which meibum could be readily expressed were graded from _____

Safety Criteria:

All patients were refracted at the qualification visit, and the best-corrected visual acuity (VA) for each eye measured using the ETDRS chart. The investigator recorded the values in Snellen equivalents. The illumination and test distance specified for the site's chart were kept constant throughout the study.

Intraocular pressure (IOP) was measured in millimeters of mercury (mm Hg) using Goldmann applanation tonometry.

Biomicroscopy was performed using slit lamp examination without pupil dilation. The examination included evaluations of _____

_____ Observations were graded on a scale of 0

(none) to +4 (very severe), with half-grade increments accepted (excluding anterior chamber cells).

Pharmacokinetic parameters were obtained for subsets of subjects in selected centers.

Schedule of Visits and Measurements (continued)

Patient Disposition and Demographics

405 patients were enrolled – 135 in the 0.05% cyclosporine group, 134 in the 0.1% cyclosporine group, and 136 in the common vehicle group.

For the 6-month Vehicle-Controlled Masked Treatment Phase, the first patient was enrolled in July 1997. Last patient exited this phase June 1998.

306 patients finished the Vehicle-Controlled Masked Treatment Phase (306/406 or 75.6%). 99 patients discontinued the protocol – 30 due to adverse events, 2 due to lack of efficacy, and 67 due to other reasons.

Table 5
Patient Disposition
ITT Population

	0.05% Cyclosporine	0.1% Cyclosporine	Vehicle	Overall
Enrolled	135	134	136	405
Completed Masked Tx Phase	107 (79.3%)	103 (76.9%)	96 (70.6%)	306 (75.6%)
D/C Masked Tx Phase	28 (20.7%)	31 (23.1%)	40 (29.4%)	
Reasons for Discontinuation				
Lack of Efficacy	0 (0%)	0 (0%)	2 (1.5%)	2 (0.5%)
Adverse Event	9 (6.7%)	15 (11.2%)	6 (4.4%)	30 (7.4%)
Pregnancy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lost to Follow-up	3 (2.2%)	0 (0%)	7 (5.1%)	10 (2.5%)
Relocated	2 (1.5%)	0 (0%)	2 (1.5%)	4 (1.0%)
Personal Reasons	4 (3.0%)	7 (5.2%)	4 (2.9%)	15 (3.7%)
Improper Entry	6 (4.4%)	5 (3.7%)	10 (7.4%)	21 (5.2%)
Non-Compliance	1 (0.7%)	2 (1.5%)	1 (0.7%)	4 (1.0%)
Prohibited Meds Used	2 (1.5%)	1 (0.7%)	4 (2.9%)	7 (1.7%)
Sponsor Terminated	0 (0%)	1 (0.7%)	0 (0%)	1 (0.2%)
Other	1 (0.7%)	0 (0%)	4 (2.9%)	5 (1.2%)

Autoantibody Tests

Sjögren's patients were defined as _____

Table 6
Demographics – Age, Race, Sex, Eye Color
ITT Population

Parameter	Study 192371-002			Study 192371-003		
	CsA 0.05%	CsA 0.1%	Vehicle	CsA 0.05%	CsA 0.1%	Vehicle
Age, N	135	134	136	158	158	156
Mean (SD), years	58.3	59.2	60.5	59.1	60.8	59.3
Range	22.8 - 90.3	21.6 - 86.7	24.7 - 88.8	24.0 - 86.5	28.1 - 89.0	27.5 - 90.3
Race, N (%)						
Caucasian	107 (79.3)	103 (76.9)	102 (75.0)	146 (92.4)	140 (88.6)	142 (91.0)
Black	4 (3.0)	7 (5.2)	9 (6.6)	4 (2.5)	9 (5.7)	6 (3.8)
Asian	5 (3.7)	5 (3.7)	6 (4.4)	3 (1.9)	1 (0.6)	0 (0.0)
Hispanic	18 (13.3)	19 (14.2)	18 (13.2)	5 (3.2)	7 (4.4)	8 (5.1)
Other	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)	0 (0.0)
Sex, N (%)						
Male	21 (15.6)	31 (23.1)	35 (25.7)	28 (17.7)	23 (14.6)	24 (15.4)
Female	114 (84.4)	103 (76.9)	101 (74.3)	130 (82.3)	135 (85.4)	132 (84.6)
Iris Color, N (%)						
Blue	41 (30.4)	37 (27.6)	45 (33.1)	56 (35.4)	58 (36.7)	64 (41.0)
Brown	65 (48.1)	64 (47.8)	66 (48.5)	61 (38.6)	63 (39.9)	50 (32.1)
Green	7 (5.2)	14 (10.4)	3 (2.2)	13 (8.2)	12 (7.6)	15 (9.6)
Hazel	22 (16.3)	18 (13.4)	22 (16.2)	26 (16.5)	20 (12.7)	24 (15.4)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Other	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.3)	3 (1.9)	3 (1.9)
Sjogren's patient	28.1% (38/135)	29.1% (39/134)	27.2% (37/136)	36.7% (58/158)	27.8% (44/158)	34.6% (54/156)

Note: CsA = cyclosporine ophthalmic emulsion, SD = standard deviation
Percentage (number) of patients with a positive response for ocular symptoms, oral symptoms, and Schirmer, and a positive response for at least one of the autoantibodies

Reviewer's Comments

Treatment groups were balanced with respect to age, sex, race, iris color, weight, and height. There were no statistically significant treatment group differences or treatment-by-investigator interactions for these demographic categories.

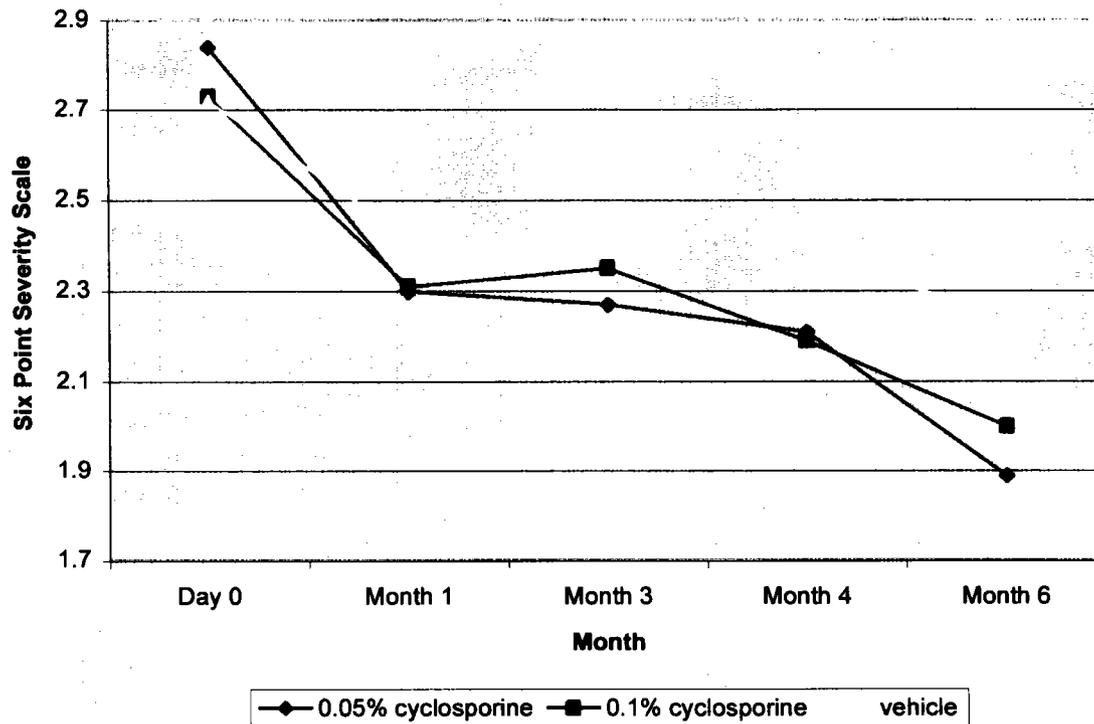
8.1.1 Efficacy – Objective Signs and Subjective Symptoms

Reviewer's Comments:

Intent-to-treat population unless noted.

Objective Signs

Corneal Staining



Reviewer's Comments:

Corneal Staining

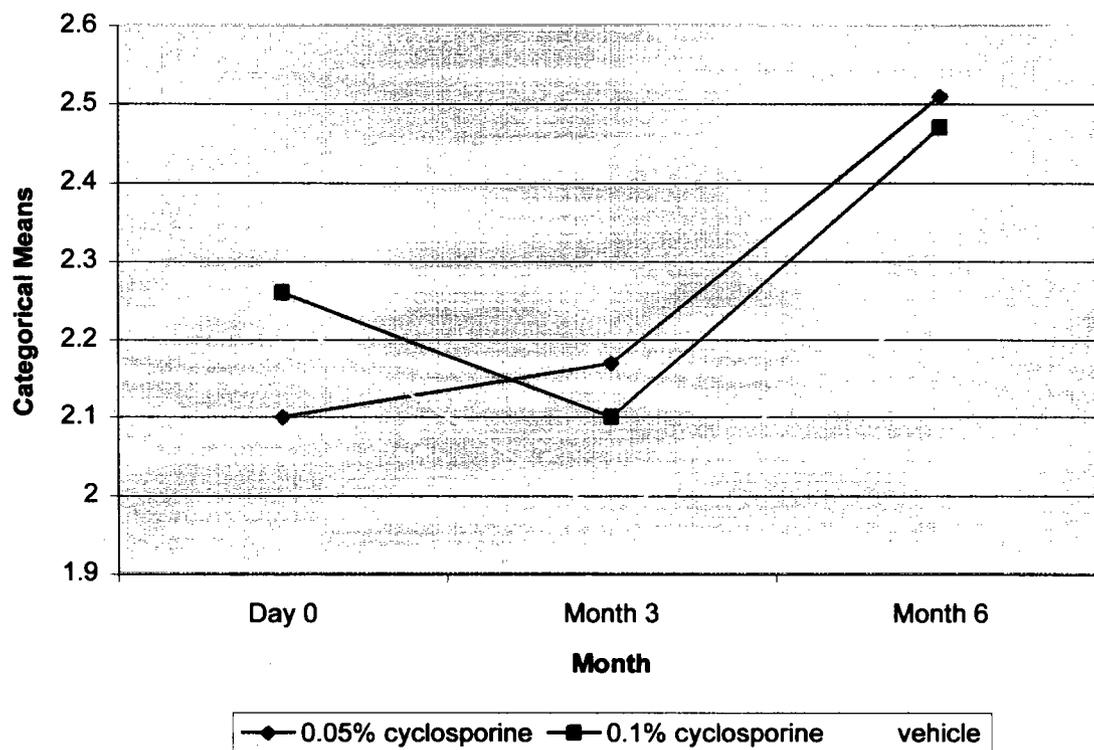
A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline in each treatment group at each visit.

Either concentration of cyclosporine showed greater improvement than vehicle at all time points.

There is a statistically significant among-group difference at month 6, favoring 0.05% cyclosporine over vehicle ($p = 0.008$).

Categorized Schirmer w/ Anesthesia



Reviewer's Comments:

Categorized Schirmer with Anesthesia

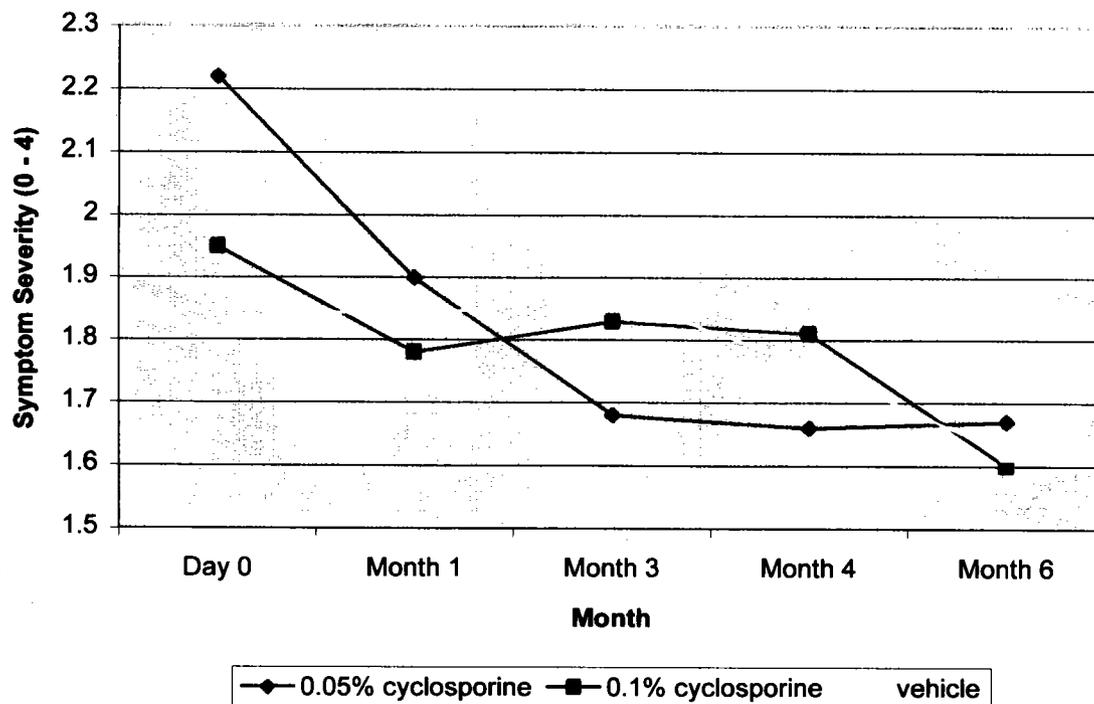
*A positive change from baseline indicates improvement.
Schirmer values were categorized from*

There is a statistically significant improvement from baseline in the 0.05% cyclosporine group at month 6.

A statistically significant among-group difference is approached but not reached at month 6, favoring 0.05% cyclosporine over vehicle ($p = 0.066$).

Subjective Symptoms

Blurred Vision - Symptom Severity



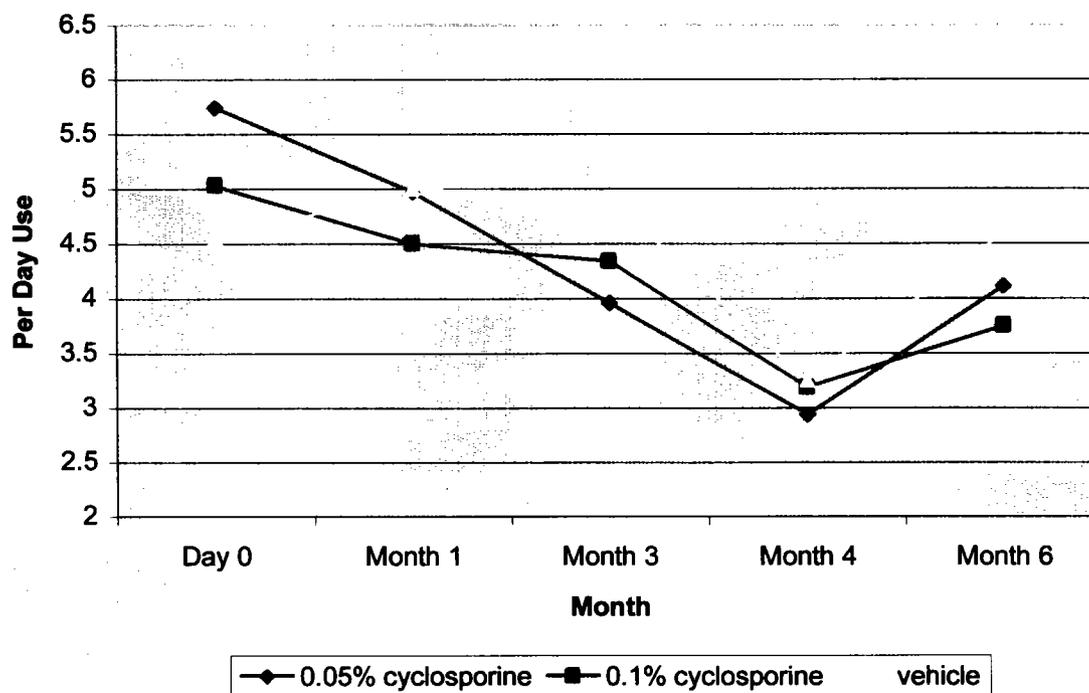
Reviewer's Comments:

Blurred Vision

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline with 0.05% cyclosporine at each visit.

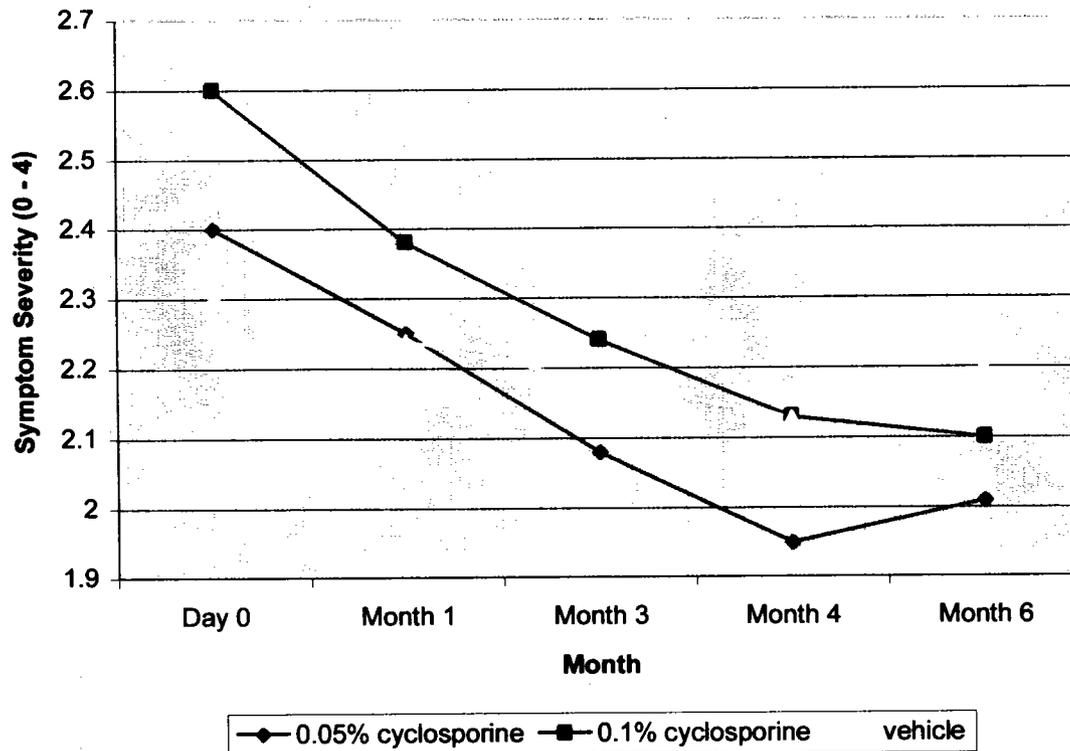
There are statistically significant among-group differences at months 3 and 4, favoring 0.05% cyclosporine over vehicle ($p = < 0.001$ and 0.003).

Refresh Use (Patient Report)**Reviewer's Comments:****Refresh Use**

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline in the 0.05% group at each visit.

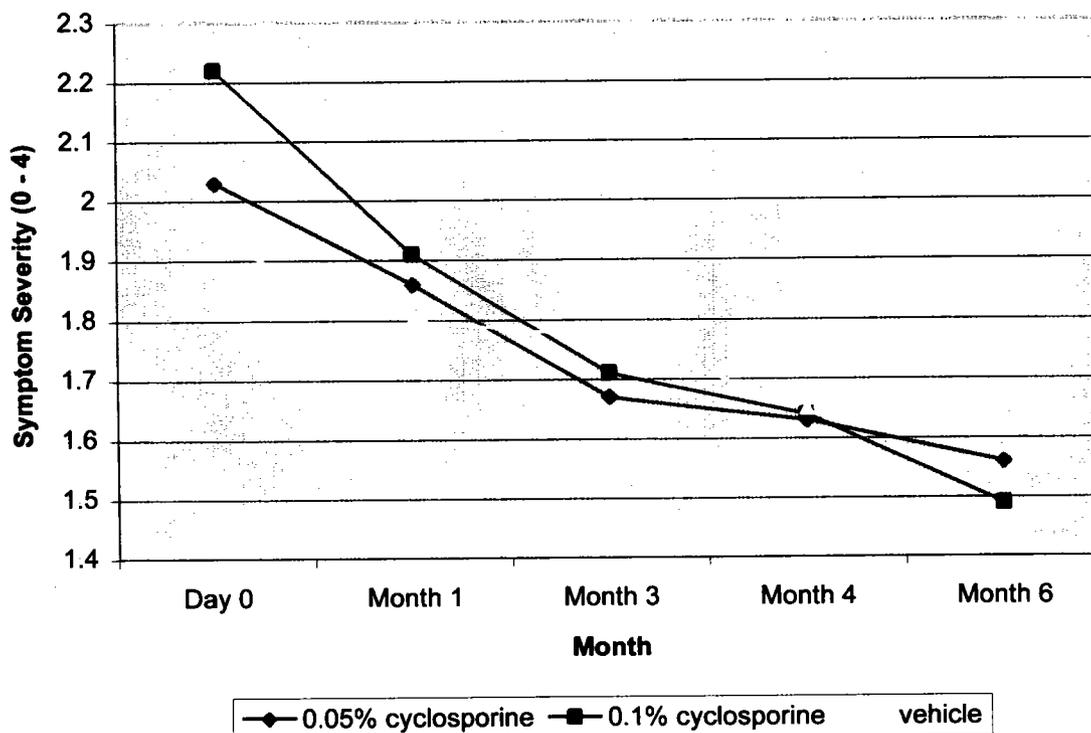
There is a statistically significant among-group difference at month 3, favoring 0.05% cyclosporine over vehicle ($p = 0.028$).

Sensitivity to Light - Symptom Severity**Reviewer's Comments:****Sensitivity to Light**

A negative change from baseline indicates improvement.

There are statistically significant among-group differences at months 4 and 6, favoring 0.01% cyclosporine over vehicle ($p = 0.020$ and 0.008).

Itching - Symptom Severity



Reviewer's Comments:

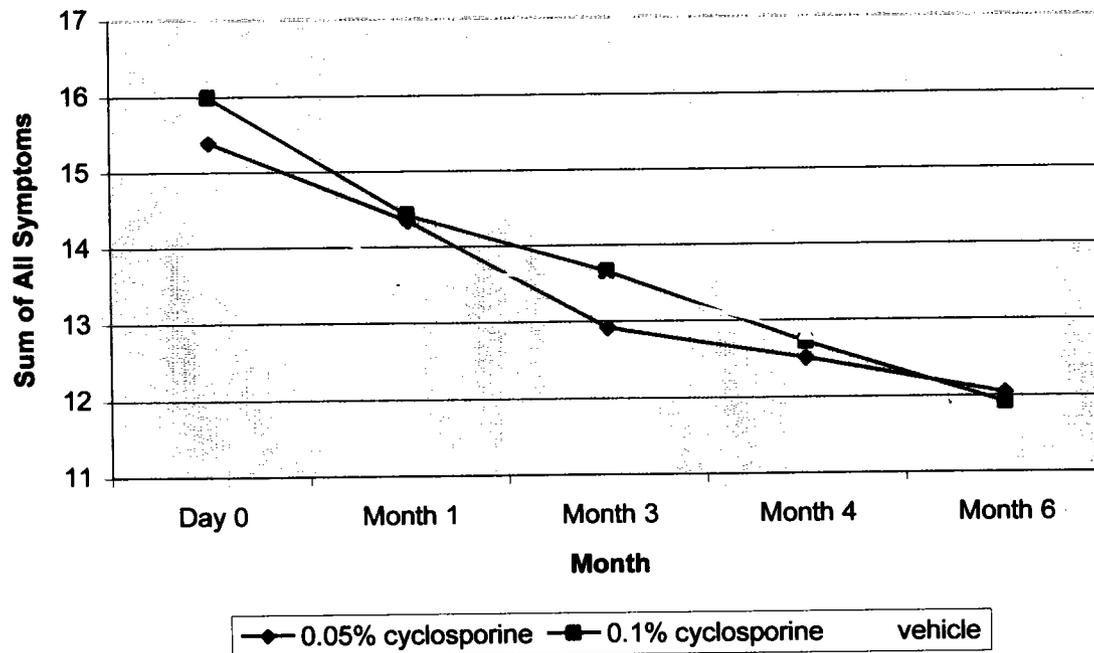
Itching

A negative change from baseline indicates improvement.

Both 0.05% and 0.1% cyclosporine showed statistically significant improvement from baseline at months 3, 4, and 6.

There are statistically significant among-group differences at months 3, 4, and 6, favoring 0.1% cyclosporine over vehicle ($p = 0.005, 0.035, \text{ and } 0.004$).

Composite Score - Symptom Severity



Reviewer's Comments:

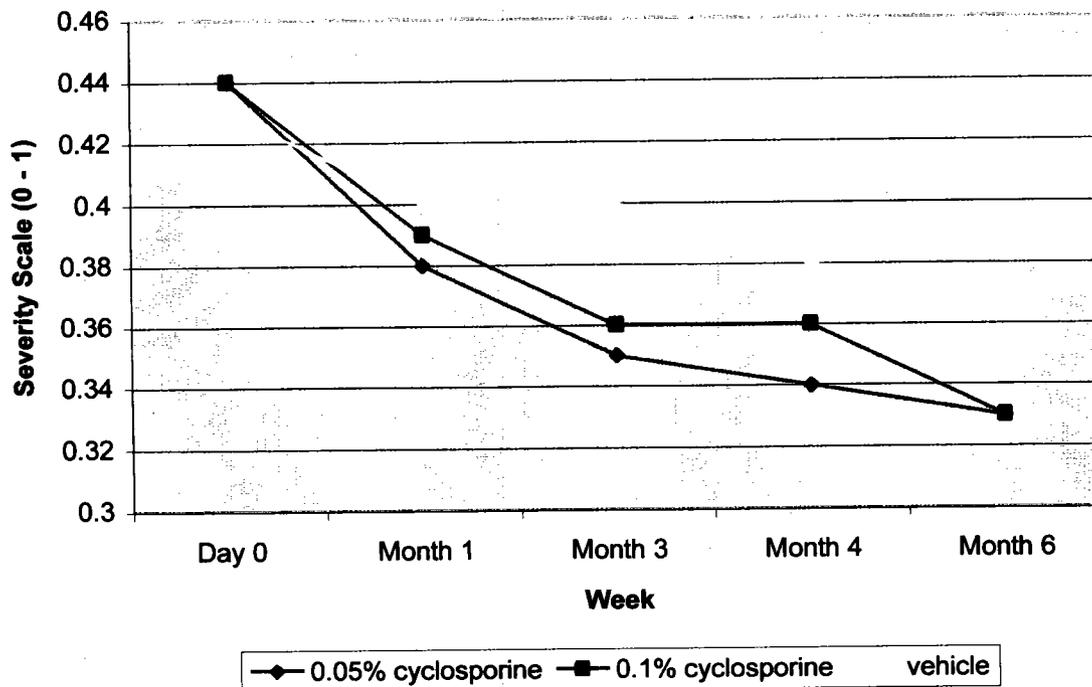
Composite Symptom Score

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline in each treatment group at each visit.

There are statistically significant among-group differences at months 3 and 6, favoring both 0.05% and 0.1% cyclosporine over baseline ($p = 0.024, 0.008$).

Ocular Surface Disease Index



Reviewer's Comments:

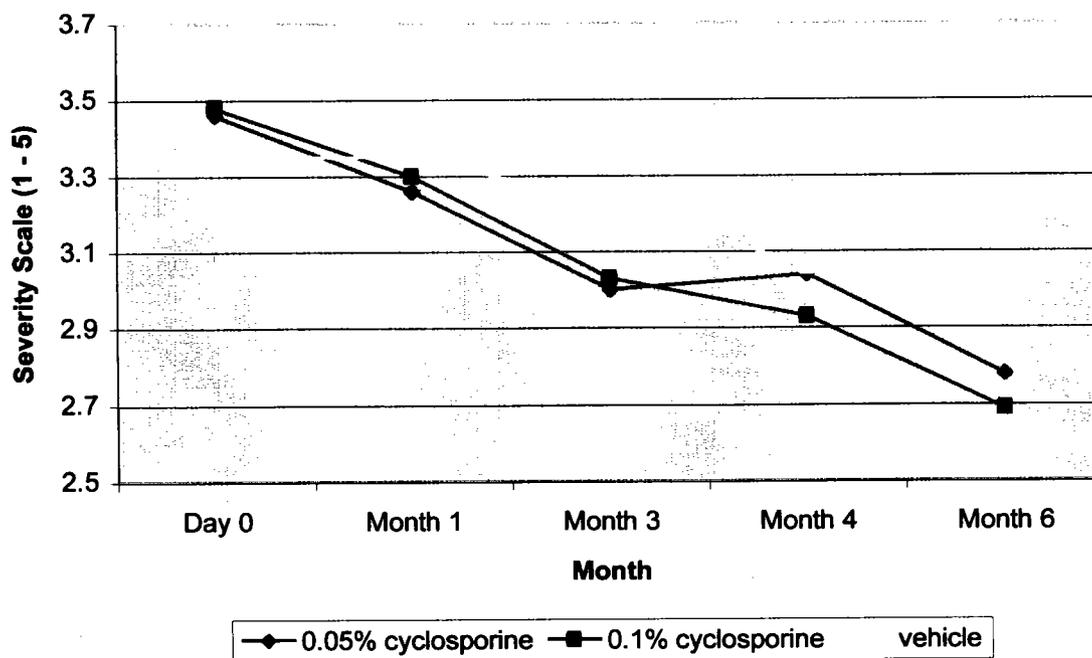
Ocular Surface Disease Index

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline at all visits in the 0.05% and 0.1% cyclosporine groups.

There are statistically significant among-group differences at months 3 and 4, favoring 0.05% cyclosporine over vehicle ($p = 0.046, 0.045$).

Facial Expression Subjective Scale



Reviewer's Comments:

Facial Expression Subjective Scale

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline at all visits in the 0.05% and 0.1% cyclosporine groups.

There are statistically significant among-group differences at months 3 and 6, favoring 0.1% cyclosporine over vehicle ($P = 0.019, 0.044$).

Other Subjective Symptoms

There are no statistically significant among-group differences found for the symptoms of 1) stinging/burning, 2) sandy or gritty feeling, 3) dryness, or 4) pain.

There was disparity in the Investigator's Evaluation of Global Response to Treatment. Some investigators rated global response based on their clinical evaluations of the patients while other investigators queried their patients directly about their response to treatment. Among-group differences in Global Response were statistically significant at month 4 for 0.1% cyclosporine ($p \leq 0.046$) and month 6 for 0.05% and 0.1% ($p \leq 0.046$). Because of the disparity in how investigators recorded and rated this response, these results and the Treatment Success results generated from them are not easily interpreted.

Responder Analysis

An analysis of responders was performed on the ITT population. Responders were defined by _____

Reviewer's Comments:**Responder Analysis**

There is an among-group difference at month 6 ($p = 0.014$) which favors 0.05% cyclosporine over vehicle.

See the comments concerning responder analysis in Section 1.2, Study #2, Protocol 192371-003.

Subgroup Analyses

Analyses were performed for the following subgroups: severe, per protocol, Sjögren's syndrome, age, sex, race, and iris color. These analyses support the intent-to-treat population.

Patients with Sjögren's syndrome were identified as those

There were no statistically significant treatment group differences or treatment-by-investigator interactions for demographics in this subgroup.

8.1.1 Safety

Visual Acuity

Visual Acuity at Month 6

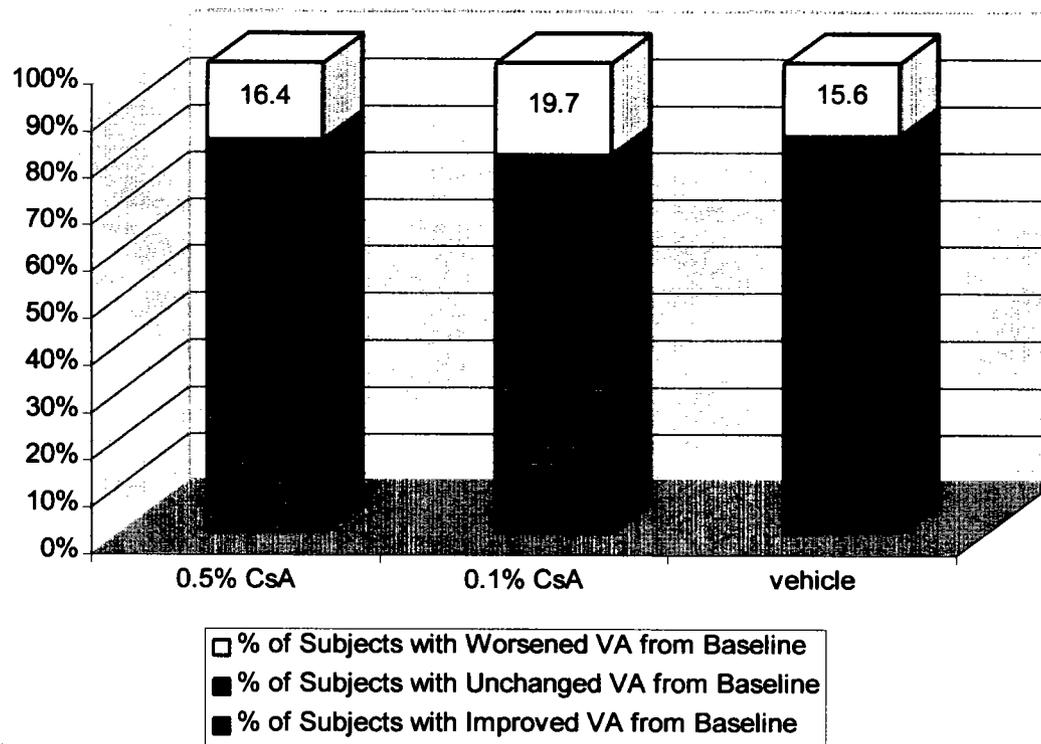


Table 7
Worsening of Baseline VA by More than 3 Lines

Reviewer's Comments:

Changes from baseline visual acuity were similar across the three treatment groups.

IOP

IOP (average of both eyes) was similar across the 3 treatment groups at baseline. There were statistically significant ($P \leq 0.031$) increases in IOP from baseline to month 6 in all 3 treatment groups; however, the mean increases were less than 1 mm Hg and not clinically relevant. The among-group difference at month 6 was not statistically significant.

Biomicroscopy

Changes in biomicroscopic findings:

_____) from baseline were similar across the 3 treatment groups. The majority of patients in each treatment group showed no change in any parameter at any follow-up visit.

Only nine patients had very severe (grade 4) biomicroscopy ratings at any follow-up visit in any category, and these were evenly divided among vehicle and cyclosporine treatment arms.

Reviewer's Comments:

There were no clinically significant among-group differences in visual acuity, IOP, or biomicroscopy.

Pharmacokinetic Results

During the Vehicle-Controlled Masked Treatment Phase, 338 blood samples were assayed for trough cyclosporine A concentrations: 131 samples at Day 0, 113 samples at month 1, and 94 samples at month 6.

Trough blood concentrations of cyclosporine A were below the limit of quantitation (BLQ) of 0.1 ng/mL at all visits for all patients in the vehicle group (112 samples) and at all visits for all patients in the 0.05% cyclosporine group (113 samples).

Trough blood concentrations of cyclosporine A were quantifiable in only 6 samples from 6 different patients in the 0.1% cyclosporine group: _____ month 1, and _____ Concentrations were BLQ at all other visits and for all other patients in the 0.1% cyclosporine group (107 samples).

Mean trough blood concentrations of cyclosporine A were BLQ in the vehicle, 0.05% and 0.1% cyclosporine emulsion groups at day 0, month 1 and month 6. Comparison of the trough blood concentrations after 1 and 6 months treatment indicated no detectable accumulation during multiple ocular dosing.

Adverse Events Monitoring

Table 8
Number (%) of Patients with Adverse Events Reported $\geq 3\%$, Regardless of Causality

COSTART body system/ Preferred term	0.05% Cyclosporine N=135 (%)	0.1% Cyclosporine N=134 (%)	Vehicle N=136 (%)
Body as a whole			
Infection	7 (5.2)	7 (5.2)	11 (8.1)
Flu syndrome	5 (3.7)	4 (3.0)	9 (6.6)
Headache	5 (3.7)	3 (2.2)	4 (2.9)
Respiratory			
Infection sinus	4 (3.0)	3 (2.2)	7 (5.1)
Bronchitis	0 (0.0)	4 (3.0)	5 (3.7)
Special senses			
Burning eye	23 (17.0)	29 (21.6)	12 (8.8)
Foreign body sensation	7 (5.2)	2 (1.5)	4 (2.9)
Discharge eye	5 (3.7)	4 (3.0)	3 (2.2)
Pruritus eye	5 (3.7)	6 (4.5)	5 (3.7)
Stinging eye	5 (3.7)	6 (4.5)	2 (1.5)
Visual disturbance	5 (3.7)	6 (4.5)	8 (5.9)
Conjunctival hyperemia	2 (1.5)	4 (3.0)	1 (0.7)
Epiphora	1 (0.7)	5 (3.7)	0 (0.0)
Eye pain	1 (0.7)	11 (8.2)	2 (1.5)

The most common ocular adverse event was burning, which appeared to be dose-related and was reported for 17.0% (23/135) of patients treated with 0.05% cyclosporine, 21.6% (29/134) of those treated with 0.1% cyclosporine, and 8.8% (12/136) of those treated with vehicle. Other ocular adverse events reported by 3% to 8% of patients in either of the cyclosporine groups (in order of decreasing incidence) were eye pain, pruritus, stinging, visual disturbance (most often blurring), discharge, foreign body sensation, conjunctival hyperemia, and epiphora. Other ocular adverse events reported by 3% to 6% of patients in the vehicle group were visual disturbance, irritation, and pruritus.

Serious Adverse Events

Table 9
Serious Adverse Events Regardless of Causality: Patient Listing

8.1.1 Reviewer's Summary of Efficacy and Safety:

There are statistically significant among-group differences favoring cyclosporine over vehicle in at least one objective sign and at least one subjective symptom. This satisfies protocol criteria for efficacy.

Adverse experiences appear mostly limited to mild to moderate ocular events. There were no increases in the occurrence of systemic or ocular infections.

8.1.2 Study #2 Protocol 192371-003

Title: A Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study of the Safety and Efficacy of Cyclosporine 0.5% and 0.1% Ophthalmic Emulsions Used Twice Daily for Up to One Year in Patients with Moderate to Severe Keratoconjunctivitis Sicca

Objective: To evaluate the safety and efficacy of cyclosporine 0.05% and 0.1% ophthalmic emulsions compared with vehicle in patients with moderate to severe keratoconjunctivitis sicca (KCS).

Study Design: Study design was identical to Study #1, Protocol 192371-002 except that pharmacokinetic parameters were not obtained.

Test Drug Schedule: Identical to Study #1, Protocol 192731-002.

Principal Investigator	Investigator Number	No. of Patients Enrolled			Patient Numbers
		Vehicle	Cyclosporine		
			0.05%	0.1%	
	1052	1	1	1	422, 423, 425
	2696	9	10	9	293-301; 392-394; 404-406; 416-421; 464-466; 581-583; a596

Principal Investigator	Investigator Number	No. of Patients Enrolled			Patient Numbers
		Vehicle	Cyclosporine		
			0.05%	0.1%	
	2798	4	4	5	278-283; 428-430; 573-574; 599
	0416	4	4	4	311-319; 488-490
	0200	3	3	3	221-229
	0470	6	6	6	302-310; 407-415
	0286	6	6	6	326; 395-403; 497-505
	2711	1	1	1	212-214
	2703	1	1	1	269-271

Principal Investigator	Investigator Number	No. of Patients Enrolled			Patient Numbers
		Vehicle	Cyclosporine		
			0.05%	0.1%	
	2704	10	9	9	101-115; 218; 353-361; 389-391
	1438	10	9	10	521-532; 560-571; 590-594
	1634	Same as above	Same as above	Same as above	Same as above
	1734	11	12	12	128; 144-148; 173-187; 329-330; 380-388; 437-439
	2821	4	5	4	533-544; 587
	1485	15	15	15	260-268; 344-352; 467-487; 575-577; 584-586
	1796	7	9	8	129-137; 230-244
	1272	5	5	4	272-276; 284-292

Principal Investigator	Investigator Number	No. of Patients Enrolled			Patient Numbers
		Vehicle	Cyclosporine		
			0.05%	0.1%	
	2794	15	13	14	138-143; 161-163; 332-343; 458-460; 491-496; 512-520; 602-604
	0369	7	6	6	188-202; 431-434
	2091	12	12	12	245-259; 440-457; 557-559
	1838	6	6	6	116-127; 320-325
	2057	9	10	10	164-172; 371-379; 461-463; 545-552
	2710	5	5	5	149-160; 578-580
	2298	5	6	6	203-211; 362-369

8.1.2 Study Design

Study design was identical to Study #1, Protocol 192371-002 except that pharmacokinetic parameters were not obtained.

Study Medications:

Identical to Study #1, Protocol 192731-002 (review page 8)

Study Masking:

Identical to Study #1, Protocol 192731-002 (review page 9)

Inclusion Criteria:

Identical to Study #1, Protocol 192731-002 (review page 9)

Exclusion Criteria:

Identical to Study #1, Protocol 192731-002 (review page 10)

Efficacy Criteria:

Identical to Study #1, Protocol 192731-002 (review page 12)

Sponsor must show a statistically significant difference between the active treatment and vehicle for 1 objective sign and 1 subjective symptom.

Safety Criteria:

Identical to Study #1, Protocol 192731-002 (review page 14)

Table 10
Schedule of Visits and Measurements



|--|--|--|--|--|--|--|--|

Patient Disposition and Demographics

472 patients were enrolled – 158 in the 0.05% cyclosporine group, 158 in the 0.1% cyclosporine group, and 156 in the common vehicle group.

For the 6-month Vehicle-Controlled Masked Treatment Phase, the first patient was enrolled in August 1997. Last patient exited this phase September 1998.

365 patients finished the Vehicle-Controlled Masked Treatment Phase (365/472 or 77.3%). 107 patients discontinued the protocol – 31 due to adverse events, 5 due to lack of efficacy, and 71 due to other reasons.

Table 11
Patient Disposition
ITT Population

	0.05% Cyclosporine	0.1% Cyclosporine	Vehicle	Overall
Enrolled	158	158	156	472
Completed Masked Tx Phase	128 (81.0%)	115 (72.8%)	122 (78.2%)	365 (77.3%)
D/C Masked Tx Phase	30 (19.0%)	43 (27.2%)	34 (21.8%)	107 (22.7%)
Reasons for Discontinuation				
Lack of Efficacy	1 (0.6%)	3 (1.9%)	1 (0.6%)	5 (1.1%)
Adverse Event	10 (6.3%)	14 (8.9%)	7 (4.5%)	31 (6.6%)
Pregnancy	0 (0%)	0 (0%)	1 (0.6%)	1 (0.2%)
Lost to Follow-up	1 (0.6%)	3 (1.9%)	4 (2.6%)	8 (1.7%)
Relocated	1 (0.6%)	0 (0%)	1 (0.6%)	2 (0.4%)
Personal Reasons	5 (3.2%)	7 (4.4%)	5 (3.2%)	17 (3.6%)
Improper Entry	6 (3.8%)	6 (3.8%)	9 (5.8%)	21 (4.4%)
Non-Compliance	3 (1.9%)	4 (2.5%)	2 (1.3%)	9 (1.9%)
Prohibited Meds Used	1 (0.6%)	3 (1.9%)	4 (2.6%)	8 (1.7%)
Sponsor Terminated	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	2 (1.3%)	3 (1.9%)	0 (0%)	5 (1.1%)

Autoantibody Tests

Table 12
Demographics – Age, Race, Sex, Eye Color
ITT Population

Parameter	Study 192371-002			Study 192371-003		
	CsA 0.05%	CsA 0.1%	Vehicle	CsA 0.05%	CsA 0.1%	Vehicle
Age, N	135	134	136	158	158	156
Mean (SD), years	58.3	59.2	60.5	59.1	60.8	59.3
Range	22.8 - 90.3	21.6 - 86.7	24.7 - 88.8	24.0 - 86.5	28.1 - 89.0	27.5 - 90.3
Race, N (%)						
Caucasian	107 (79.3)	103 (76.9)	102 (75.0)	146 (92.4)	140 (88.6)	142 (91.0)
Black	4 (3.0)	7 (5.2)	9 (6.6)	4 (2.5)	9 (5.7)	6 (3.8)
Asian	5 (3.7)	5 (3.7)	6 (4.4)	3 (1.9)	1 (0.6)	0 (0.0)
Hispanic	18 (13.3)	19 (14.2)	18 (13.2)	5 (3.2)	7 (4.4)	8 (5.1)
Other	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)	0 (0.0)
Sex, N (%)						
Male	21 (15.6)	31 (23.1)	35 (25.7)	28 (17.7)	23 (14.6)	24 (15.4)
Female	114 (84.4)	103 (76.9)	101 (74.3)	130 (82.3)	135 (85.4)	132 (84.6)
Iris Color, N (%)						
Blue	41 (30.4)	37 (27.6)	45 (33.1)	56 (35.4)	58 (36.7)	64 (41.0)
Brown	65 (48.1)	64 (47.8)	66 (48.5)	61 (38.6)	63 (39.9)	50 (32.1)
Green	7 (5.2)	14 (10.4)	3 (2.2)	13 (8.2)	12 (7.6)	15 (9.6)
Hazel	22 (16.3)	18 (13.4)	22 (16.2)	26 (16.5)	20 (12.7)	24 (15.4)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Other	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.3)	3 (1.9)	3 (1.9)
Sjogren's patient	28.1% (38/135)	29.1% (39/134)	27.2% (37/136)	36.7% (58/158)	27.8% (44/158)	34.6% (54/156)

Note: CsA = cyclosporine ophthalmic emulsion. SD = standard deviation

Reviewer's Comments

Treatment groups were balanced with respect to age, sex, race, iris color, weight, and height. There were no statistically significant treatment group differences or treatment-by-investigator interactions for these demographic categories.

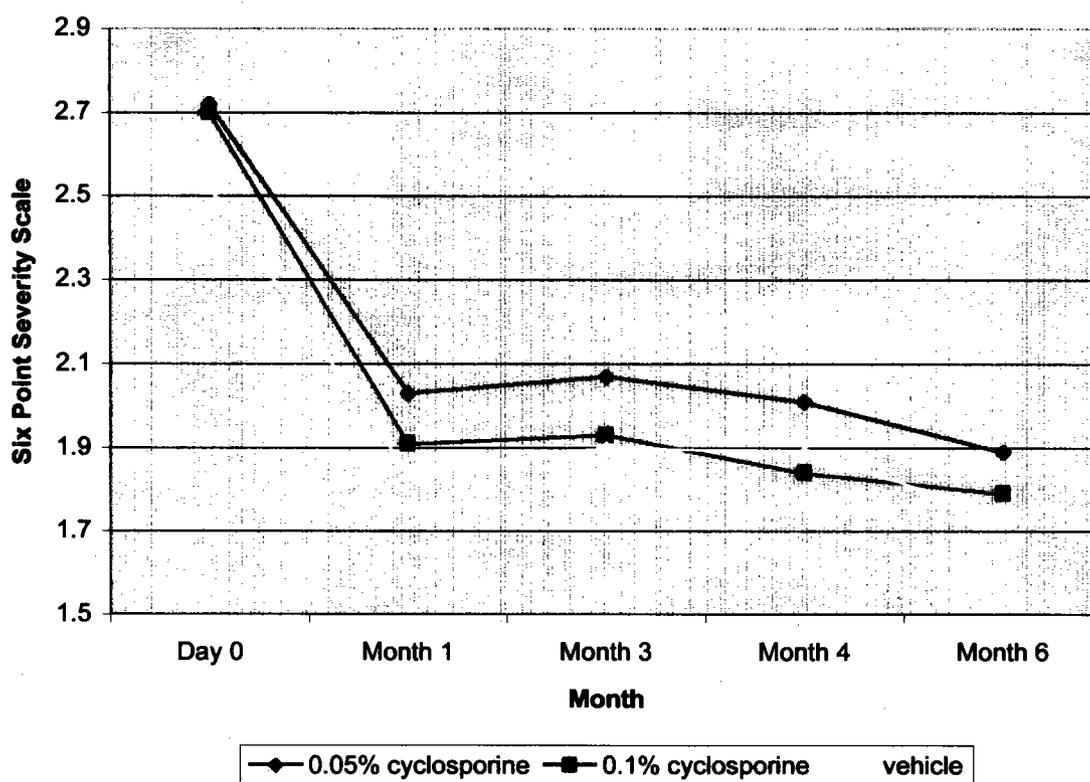
8.1.2 Efficacy – Objective Signs and Subjective Symptoms

Reviewer's Comments:

Intent-to-treat population unless noted.

Objective Signs

Corneal Staining



Reviewer's Comments:

Corneal Staining

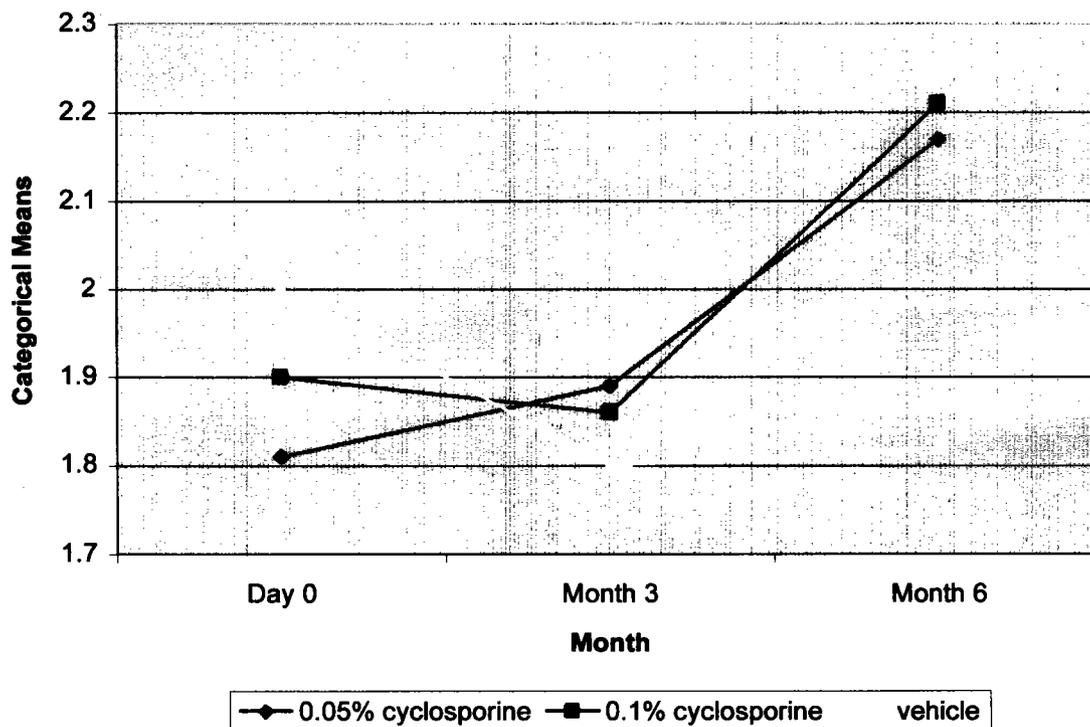
A negative change from baseline indicates improvement.

Baseline mean corneal staining scores are significantly higher in the 0.05% and 0.1% cyclosporine groups than in the vehicle group (respectively, 2.72, 2.70, and 2.52; $p = 0.036$).

There are statistically significant improvements from baseline in each treatment group at each visit.

There are no statistically significant among-group differences.

Categorized Schirmer w/ Anesthesia



Reviewer's Comments:

Categorized Schirmer with Anesthesia

A positive change from baseline indicates improvement.

There are statistically significant improvements from baseline in the 0.05% and 0.1% cyclosporine groups at month 6.

There are statistically significant among-group differences favoring both 0.05% and 0.1% cyclosporine over vehicle ($p < 0.001$).

Tear Breakup Time

Reviewer's Comments:

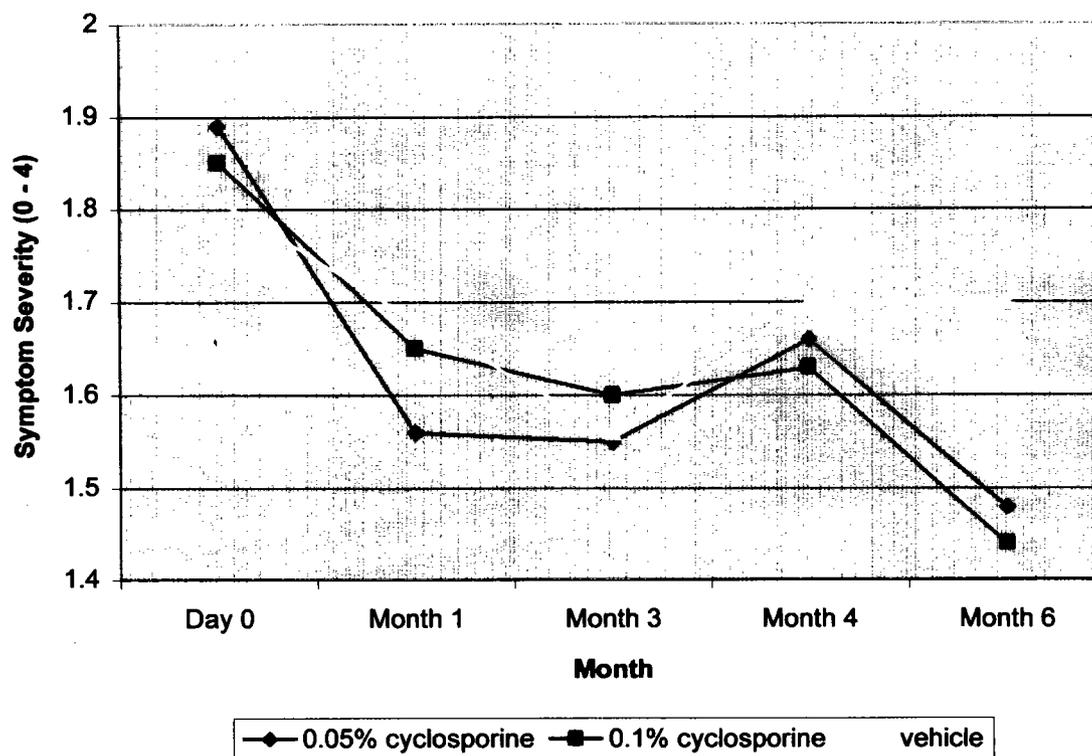
Other Objective Signs

There are no statistically significant among-group differences found for 1) _____

_____, or 4) categorized Schirmer values without anesthesia.

Statistically significant improvement from baseline ($p \leq 0.05$) was seen for all treatment groups at most follow-up visits for _____

_____) 4) categorized Schirmer values without anesthesia.

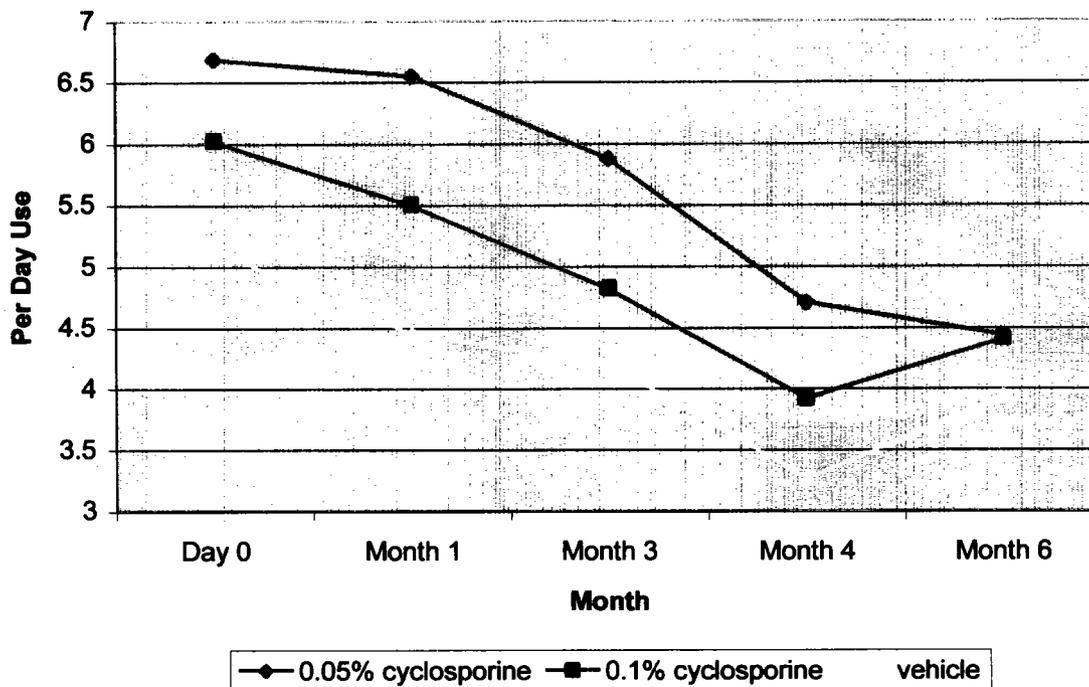
Subjective Symptoms**Blurred Vision - Symptom Severity****Reviewer's Comments:****Blurred Vision**

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline with both 0.05% and 0.1% cyclosporine at 6 months.

There are no statistically significant among-group differences

Refresh Use (Patient Report)



Reviewer's Comments:

Refresh Use

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline with 0.05% and 0.01% cyclosporine at months 4 and 6.

A statistically significant among-group difference is approached but not reached at month 6, favoring 0.05% cyclosporine over vehicle ($p = 0.087$).

**Global Response to Treatment:
Baseline and Change From Baseline**

Table 13

	0.05% cyclosporine (N=158)	0.1% cyclosporine (N=158)	Vehicle (N=156)	P value(b)
Month 1				
N	146	140	142	0.531
Completely Cleared	1 (0.7%)	0 (0.0%)	1 (0.7%)	
Almost Cleared	1 (0.7%)	3 (2.1%)	1 (0.7%)	
Marked Response	5 (3.4%)	10 (7.1%)	7 (4.9%)	
Moderate Response	27 (18.5%)	20 (14.3%)	20 (14.1%)	
Slight Response	53 (36.3%)	54 (38.6%)	54 (38.0%)	
Condition Unchanged	56 (38.4%)	47 (33.6%)	53 (37.3%)	
Condition Worsened	3 (2.1%)	6 (4.3%)	6 (4.2%)	
Month 3				
N	150	148	147	0.031
Completely Cleared	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Almost Cleared	0 (0.0%)	2 (1.4%)	1 (0.7%)	
Marked Response	3 (2.0%)	8 (5.4%)	5 (3.4%)	
Moderate Response	29 (19.3%)	33 (22.3%)	24 (16.2%)	
Slight Response	53 (35.3%)	58 (39.2%)	51 (34.7%)	
Condition Unchanged	57 (38.0%)	38 (25.7%)	60 (40.8%)	
Condition Worsened	8 (5.3%)	9 (6.1%)	6 (4.1%)	
Month 4				
N	150	148	147	0.255
Completely Cleared	1 (0.7%)	0 (0.0%)	0 (0.0%)	
Almost Cleared	3 (2.0%)	2 (1.4%)	2 (1.4%)	
Marked Response	6 (4.0%)	10 (6.8%)	11 (7.5%)	
Moderate Response	33 (22.0%)	34 (23.0%)	21 (14.3%)	
Slight Response	56 (37.3%)	46 (31.1%)	48 (32.7%)	
Condition Unchanged	44 (29.3%)	51 (34.5%)	56 (38.1%)	
Condition Worsened	7 (4.7%)	5 (3.4%)	9 (6.1%)	
Month 6				
N	151	148	147	0.364
Completely Cleared	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Almost Cleared	9 (6.0%)	4 (2.7%)	6 (4.1%)	
Marked Response	15 (9.9%)	18 (12.2%)	14 (9.5%)	
Moderate Response	26 (17.2%)	32 (21.6%)	28 (19.0%)	
Slight Response	49 (32.5%)	41 (27.7%)	50 (34.0%)	
Condition Unchanged	46 (30.5%)	45 (30.4%)	46 (31.3%)	
Condition Worsened	6 (4.0%)	8 (5.4%)	3 (2.0%)	

[a] Completely Cleared - 100% improvement; Almost Cleared - approximately 90% improvement; Marked Response - approximately 75% improvement; Moderate Response - approximately 50% improvement; Slight Response - approximately 25% improvement.

[b] Among-group p-values are from CMH test.

Reviewer's Comments:

Among-group differences are statistically significant at month 3 ($p = 0.031$). Pairwise comparisons show statistically significant greater responses for the 0.1% cyclosporine group than for the 0.05% cyclosporine and vehicle group;

There was disparity in the Investigator's Evaluation of Global Response to Treatment. Some investigators rated global response based on their clinical evaluations of the patients while other investigators queried their patients directly about their response to treatment.

Because of the disparity in how investigators recorded and rated this response, these results and the Treatment Success results generated from them are not easily interpreted.

Other Subjective Symptoms

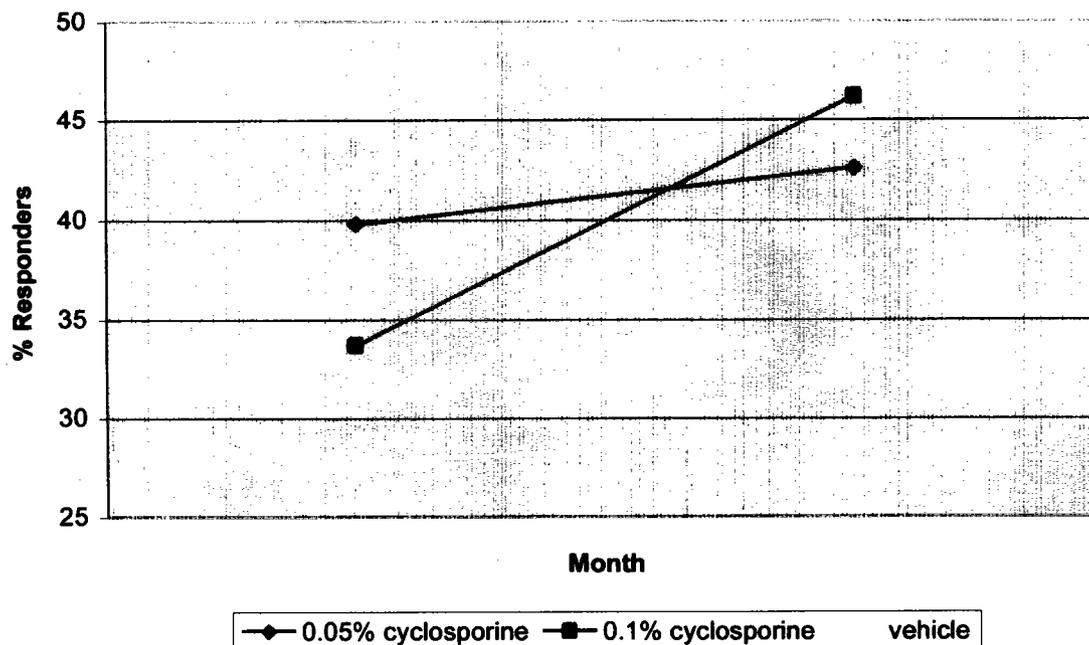
There were no statistically significant differences among the treatment groups at baseline for any of the symptoms except burning/stinging, where the mean for the 0.05% cyclosporine group was significantly higher than for vehicle (respectively, 2.32 and 2.01; $p = 0.050$).

There are no statistically significant among-group differences found for the symptoms of 1) sensitivity to light, 2) dryness, 3) sandy or gritty feeling, 4) stinging/burning, 5) pain, 6) itching, or 7) composite symptom score.

Statistically significant improvement from baseline ($p \leq 0.05$) is seen for all treatment groups at most follow-up visits for 1) sensitivity to light, 2) dryness, 3) sandy or gritty feeling, and 4) itching.

There are no statistically significant among-group differences in the Ocular Surface Disease Index or Facial Expression Subjective Scale at any time point.

Responder Analysis



Reviewer's Comments:

Responder Analysis

The responder analysis does generate an among-group difference that is statistically significant at month 6 ($p = 0.012$), with responder rates of 42.6% of patients in the 0.05% cyclosporine group, 46.2% in the 0.1% cyclosporine group, and 29.2% in the vehicle group. Pairwise comparisons are statistically significant for 0.05% and 0.1% cyclosporine vs. vehicle ($p = 0.030, 0.007$).

In reviewing the protocol, it is not clear that the responder designation was formulated prior to initiation of the study. It is certainly not a previously established objective sign or subjective symptom category for the establishment of efficacy.

Subgroup Analyses

Analyses were performed for the following subgroups: severe, per protocol, Sjögren's syndrome, age, sex, race, and iris color. These analyses support the intent-to-treat population.

Patients with Sjögren's syndrome were identified as those

There were no statistically significant treatment group differences or treatment-by-investigator interactions for demographics in this subgroup.

8.1.2 Safety Criteria:

Visual Acuity

Visual Acuity at Month 6

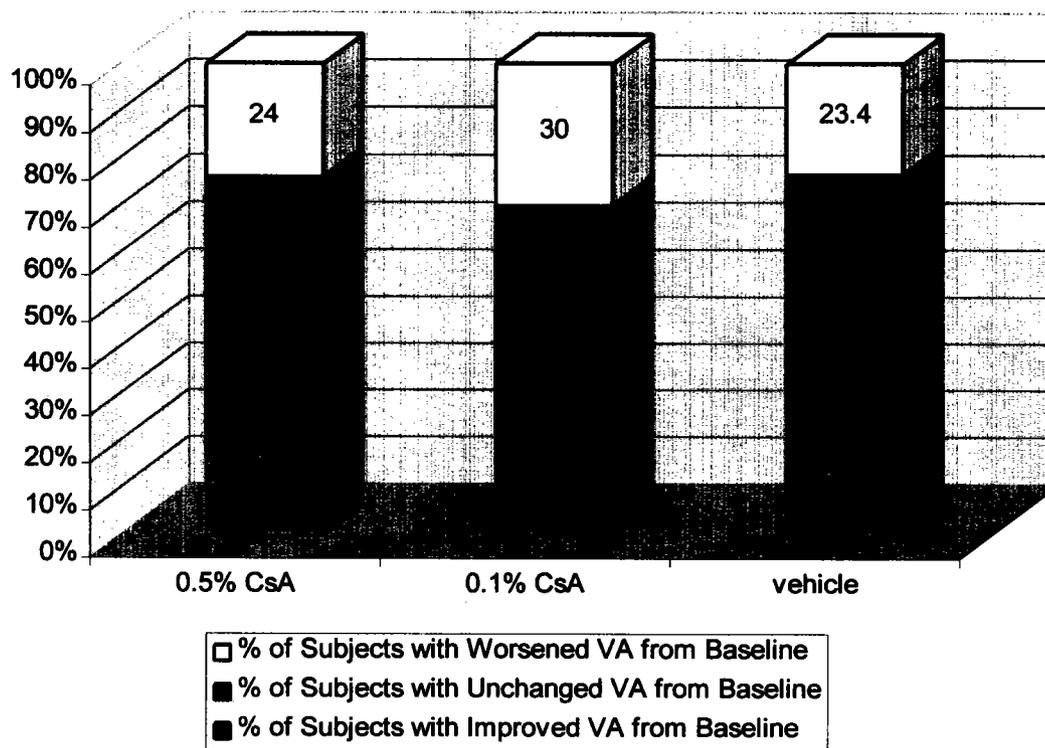


Table 14
Worsening of Baseline VA by More than 3 Lines

Reviewer's Comments:

Changes from baseline visual acuity were similar across the three treatment groups.

IOP

IOP (average of both eyes) was similar across the 3 treatment groups at baseline.

Biomicroscopy

Changes in biomicroscopic findings

_____) from baseline were similar across the 3 treatment groups. The majority of the patients in each treatment group showed no change in any parameter at any follow-up visit, with the exception of _____ where almost one-half the patients had improved from baseline to month 6.

Only seventeen patients had very severe (grade 4) biomicroscopy ratings at any follow-up visit in any category, and these were evenly divided among vehicle and cyclosporine treatment groups with the exception noted below.

Reviewer's Comments:

There were no clinically significant among-group differences in visual acuity, IOP, or biomicroscopy.

Adverse Events Monitoring

Table 15
Number (%) of Patients with Adverse Events $\geq 3\%$, Regardless of Causality

COSTART body system/ Preferred term	0.05% Cyclosporine N=158 (%)	0.1% Cyclosporine N=158 (%)	Vehicle N=156 (%)
Body as a whole			
Infection	11 (7.0)	16 (10.1)	18 (11.5)
Flu syndrome	8 (5.1)	2 (1.3)	4 (2.6)
Headache	6 (3.8)	8 (5.1)	3 (1.9)
Cardiovascular			
Hypertension	7 (4.4)	3 (1.9)	2 (1.3)
Digestive			
Periodontal abscess	2 (1.3)	5 (3.2)	1 (0.6)
Respiratory			
Bronchitis	5 (3.2)	1 (0.6)	5 (3.2)
Sinus infection	5 (3.2)	4 (2.5)	6 (3.8)
Rhinitis	5 (3.2)	2 (1.3)	3 (1.9)
Skin			
Rash	5 (3.2)	0 (0.0)	4 (2.6)
Special senses			
Burning eye	24 (15.2)	22 (13.9)	9 (5.8)
Discharge eye	9 (5.7)	3 (1.9)	5 (3.2)
Conjunctival hyperemia	9 (5.7)	8 (5.1)	1 (0.6)
Irritation eye	6 (3.8)	4 (2.5)	0 (0.0)
Photophobia	5 (3.2)	8 (5.1)	3 (1.9)
Stinging eye	5 (3.2)	8 (5.1)	3 (1.9)
Foreign body sensation	4 (2.5)	5 (3.2)	4 (2.6)
Eye pain	4 (2.5)	6 (3.8)	6 (3.8)
Visual disturbance	4 (2.5)	9 (5.7)	10 (6.4)
Pruritus	3 (1.9)	7 (4.4)	5 (3.2)

The most common ocular adverse event was burning, which was reported for 15.2% (24/158) of patients treated with 0.05% cyclosporine, 13.9% (22/158) of those treated with 0.1% cyclosporine, and 5.8% (9/156) of those treated with vehicle. Other ocular events reported by 3% to 6% of patients in either of the cyclosporine groups (in order of decreasing incidence) were conjunctival hyperemia, photophobia, stinging, visual disturbance (most often blurring), discharge, eye pain, irritation, pruritus, and foreign body sensation. Other ocular events reported by 3% to 6% of patients in the vehicle group were visual disturbance, discharge, eye pain, and pruritus.

Serious Adverse Events

Table 16
Serious Adverse Events Regardless of Causality: Patient Listing

There were 3 deaths during the study.

8.1.2 Reviewer's Summary of Efficacy and Safety:

There are statistically significant among-group differences favoring cyclosporine over vehicle in at least one objective sign and at least one subjective symptom. The subjective symptom that demonstrates statistical significance (Global Response to Treatment) appears to have been evaluated differently by different investigators. Some investigators rated global response based on their clinical evaluations of the patients while other investigators queried their patients directly about their response to treatment. The protocol does not clearly state which of these evaluations was originally intended.

Several other efficacy variables approach among-group statistical significance in Protocol 192731-001. See below.

Objective Signs Approaching Among-Group Statistical Significance*	Subjective Symptoms Approaching Among-Group Statistical Significance*
Corneal Staining Month 4 p = 0.091	Symptom Severity, Dryness Month 1 p = 0.070 Month 3 p = 0.123 Month 6 p = 0.150
	Symptom Severity, Sandy or Gritty Feeling Month 6 p = 0.106
	Symptom Severity, Blurred Vision Month 1 p = 0.210 Month 6 p = 0.263
	Refresh Use Month 6 p = 0.087

* favoring 0.05% cyclosporine over vehicle

Adverse experiences appear mostly limited to mild to moderate ocular events. There were no increases in the occurrence of systemic or ocular infections.

Table 18

Table 19

8.1.4 Study #3 Protocol 192731-001

Title: A Dose-Ranging Study Evaluating the Safety, Tolerability, and Efficacy of Cyclosporine (0.05%, 0.1%, 0.2%, 0.4%) and Vehicle Ophthalmic Emulsions in the Treatment of Moderate to Severe Keratoconjunctivitis Sicca (KCS)

Objective: To evaluate the safety, tolerability, and dose-response efficacy of cyclosporine 0.05%, 0.1%, 0.2%, and 0.4% ophthalmic emulsions compared with the vehicle of cyclosporine in patients with moderate to severe keratoconjunctivitis sicca (KCS) with or without Sjögren's Syndrome.

Study Design: A randomized, multicenter (9 sites), double-masked, parallel-group, dose-response study.

Test Drug Schedule: All subjects received either cyclosporine 0.05%, 0.1%, 0.2%, 0.4%, or vehicle of cyclosporine 0.2% emulsion bilaterally, BID for 12 weeks.

Investigators:	ID #	No. Enrolled
	(0200)	13 subjects
	(0470)	13 subjects
	(2362)	19 subjects

(1438) 24 subjects

(2363) 5 subjects

(2365) 17 subjects

(2090) 10 subjects

(2366) 33 subjects

(2057) 28 subjects

8.1.4 Study Design

This was a prospective, double-masked, randomized, parallel-group, multicenter trial in a study population of 162 subjects with keratoconjunctivitis sicca (with or without Sjögren's Syndrome). Patients with apparent _____ were excluded. Subjects were randomized to receive either cyclosporine ophthalmic emulsions 0.05%, 0.1%, 0.2%, 0.4% or vehicle of 0.2% cyclosporine ophthalmic emulsion bilaterally BID for 12 weeks.

Study Medications:

- Cyclosporine 0.05% ophthalmic emulsion (Allergan formulation number 8736X) contained: 0.05% cyclosporine _____

- Cyclosporine 0.1% ophthalmic emulsion (Allergan formulation number 8735X) contained: 0.1% cyclosporine,
- Cyclosporine 0.2% ophthalmic emulsion (Allergan formulation number 8734X) contained: 0.2% cyclosporine,
- Cyclosporine 0.4% ophthalmic emulsion (Allergan formulation number 8733X) contained: 0.4% cyclosporine
- Vehicle of cyclosporine 0.2% ophthalmic emulsion (Allergan formulation number 8747X) contained:
- Refresh® (Allergan formulation number 7447X) contains:

Study Masking:

Two unit doses were sealed in a two-compartment plastic pouch (one unit dose per compartment). Sixteen pouches were sealed in a packing box. Each pouch and box was coded with a shipment number and was labeled with the number of the subject to whom the packing boxes were given.

Each time a packing box was dispensed to a patient, the tear-off portion of the label was attached to the patient's case report form. If necessary for medical reasons, the investigator could irreversibly unmask the tear-off portion of the patient's medication label. No patient's medications were unmasked in this study.

Inclusion Criteria:

Wash-out Phase

- Male or female of legal age of consent
- Signed consent form
- Patient had to be properly motivated and willing to cooperate with the investigator by following the required medication regimen and accurately completing diary records; patient had to be willing and able to return for all visits during the study
- Female patients of childbearing potential had to use a reliable form of contraception, as determined by the investigator, during the study and for one month following the end of the study. A female was considered of childbearing potential unless she met

one of the following criteria: was post-menopausal, had no uterus, had no ovaries, or had a bilateral tubal ligation.

- A negative urine pregnancy test result for women of childbearing potential
- Normal lid anatomy and blinking function
- _____
- Diagnosis of KCS with continued objective signs despite conventional treatment, which may have included artificial tear drops, gels and ointments, sympathomimetic agents and parasympathomimetic agents

1) Schirmer (without anesthesia) _____

2) If Schirmer (without anesthesia) is _____ Schirmer with nasal stimulation \geq _____

- Corneal punctate fluorescein staining _____
- The following topical or systemic medications were allowed as long as the patient had been on a stable dose for:

At least 30 days prior to screening visit:

At least 90 days prior to screening visit:

- Estrogen-progesterone
- other estrogen derivatives

Treatment Phase

- Diagnosis of KCS with continued subjective symptoms and objective signs despite conventional management with Refresh®

1) Schirmer (without anesthesia) _____

2) If Schirmer (without anesthesia) is _____ Schirmer with nasal stimulation _____

- Corneal punctate fluoroscein staining _____
- At least one subjective symptom of ocular discomfort (burning/stinging, tearing, discharge, itching, foreign body sensation, blurred vision, dryness, photophobia, soreness/pain) _____

Exclusion Criteria:

- Concurrent involvement in any other clinical trial within the last 30 days involving an investigational drug/device or participation in a clinical trial within the last 30 days preceding the screening visit
- Female patient who was pregnant or nursing, or planning pregnancy during the study, or thought she may have been pregnant at the start of the study
- Altered level of consciousness, memory, or mental status that was expected to interfere with study compliance and diary completion
- Uncontrolled systemic disease or the presence of any significant illness that could, in the judgement of the investigator, have jeopardized patient safety or interfered with interpretation of the results of the study (specifically excluded - patients with Parkinson's)
- Required use of topical or systemic medications, less than 30 days prior to screening, which may affect dry eye. These included:
 - General anesthetics
 - Antiparkinsonian agents
- Required use of topical or systemic medications, including cyclosporine, less than 90 days prior to screening, which may affect dry eye
- Known hypersensitivity to any other components of the study or procedural medications
- KCS patients who had Schirmer readings _____ without anesthesia _____
- Contact lens wear during study
- Frank ocular infection or non-KCS inflammation
- Corneal disorder or abnormality that affected corneal sensitivity or normal spreading of the tear film (except SPK)
- Active severe blepharitis or obvious inflammation of the lid margin, which in the opinion of the investigator, may have interfered with study interpretation
- Occlusion of the lacrimal puncta (temporary or permanent) within 3 months prior to study entry
- Presence of neurotrophic corneas or history of anterior segment surgery or trauma, which could have affected corneal sensitivity (including cataract surgery)
- _____
- Required use of any concomitant ocular medication other than a standardized regimen of glaucoma medications and the artificial tears supplied by the sponsor
- History or presence of _____

Efficacy Criteria:

Primary efficacy measures were Schirmer tear test (without anesthesia), SPK, and symptoms of dry eye (from patient's diaries and CRF queries).

Safety Criteria:

Safety variable evaluated during the study were vital signs, visual acuity, IOP, biomicroscopy, conjunctival microbiology (at four selected study centers), CBC, blood chemistry, whole blood cyclosporine concentrations, and adverse events monitoring.

Table 20
Schedule of Visits and Measurements

Key to Abbreviations

Subject Disposition and Demographics

The target sample size was 30 evaluable patients enrolled per treatment group (total = 150). 162 subjects were enrolled – 31 in the 0.05% cyclosporine group, 32 in the 0.1% cyclosporine group, 34 in the 0.2% cyclosporine group, 32 in the 0.4% cyclosporine group, and 33 in the vehicle group.

First patient enrolled May 1995. Last patient exited February 1996.

150 subjects completed the protocol (completed treatment and post-treatment phase as planned). 12 subjects discontinued the protocol - four due to adverse events, three due to personal reasons, one due to noncompliance, one due to concomitant therapy, one due to missed visits, one due to baseline elevated serum creatinine, and one subject voluntarily exited.

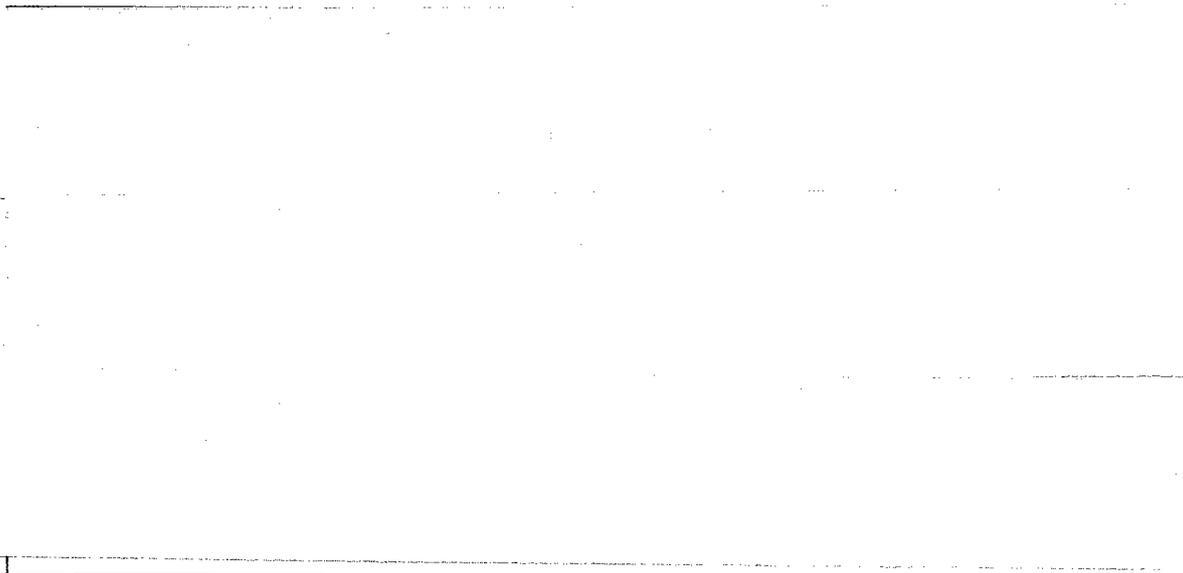


Table 21
Demographics – Age, Race, Sex, Eye Color
ITT Population

Parameter	Vehicle	Cyclosporine				Total
		0.05%	0.1%	0.2%	0.4%	
Age, N	33	31	32	34	32	162
Mean (SD), years	61.2	58.5	56.5	58.0	58.9	58.6
Range	37.7 - 87.7	35.7 - 80.0	39.5 - 75.9	31.4 - 75.1	33.0 - 82.4	31.4 - 87.7
Race, N (%)						
White	28 (84.8)	28 (90.3)	27 (84.4)	33 (97.1)	29 (90.6)	145 (89.5)
Black	3 (9.1)	3 (9.7)	3 (9.4)	1 (2.9)	2 (6.3)	12 (7.4)
Asian	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hispanic	1 (3.0)	0 (0.0)	2 (6.3)	0 (0.0)	1 (3.1)	4 (2.5)
Sex, N (%)						
Male	5 (15.2)	4 (12.9)	3 (9.4)	5 (14.7)	9 (28.1)	26 (16.0)
Female	28 (84.8)	27 (87.1)	29 (90.6)	29 (85.3)	23 (71.9)	136 (84.0)
Iris Color, N (%)						
Blue	10 (30.3)	9 (29.0)	9 (28.1)	12 (35.3)	11 (34.4)	51 (31.5)
Brown	13 (39.4)	12 (38.7)	17 (53.1)	12 (35.3)	11 (34.4)	65 (40.1)
Green	6 (18.2)	3 (9.7)	0 (0.0)	3 (8.8)	5 (15.6)	17 (10.5)
Black	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hazel	4 (12.1)	6 (19.4)	6 (18.8)	7 (20.6)	4 (12.5)	27 (16.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.6)

Note: SD = standard deviation

Reviewer's Comments:

There were no statistically significant among-group differences for any of the above demographic categories.

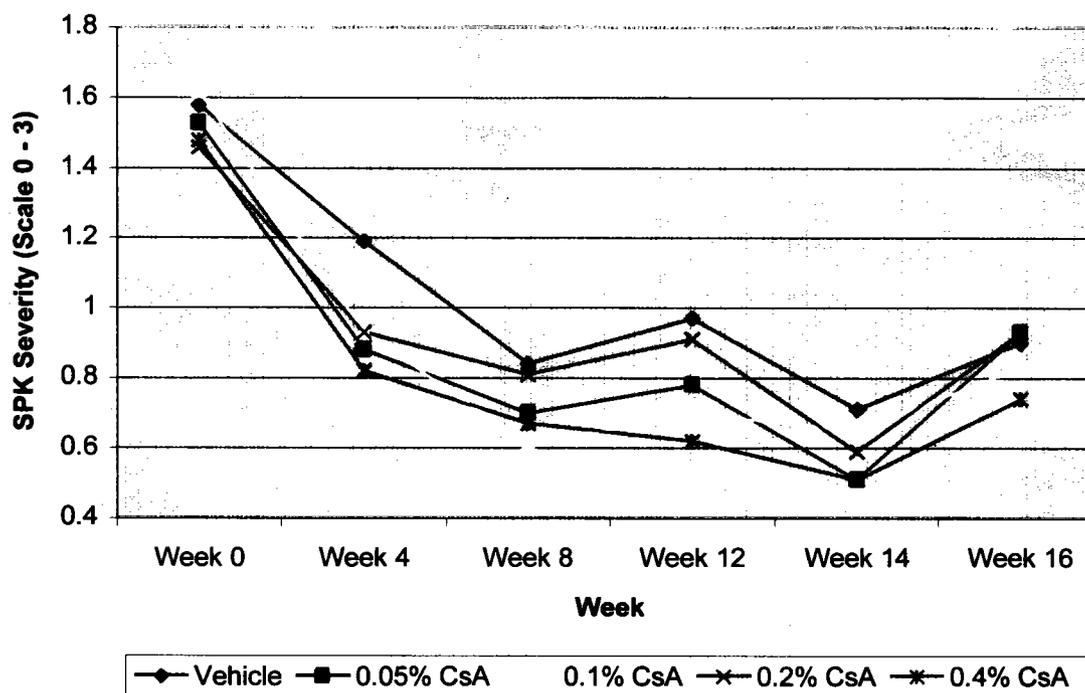
8.1.4 Efficacy – Primary Efficacy Measures and Secondary Efficacy Measures

Reviewer's Comments:

Intent-to-treat population unless noted. Weeks 14 and 16 constitute the 4-week post-treatment phase.

Primary Efficacy Measures

SPK - Corneal Staining



Reviewer's Comments:

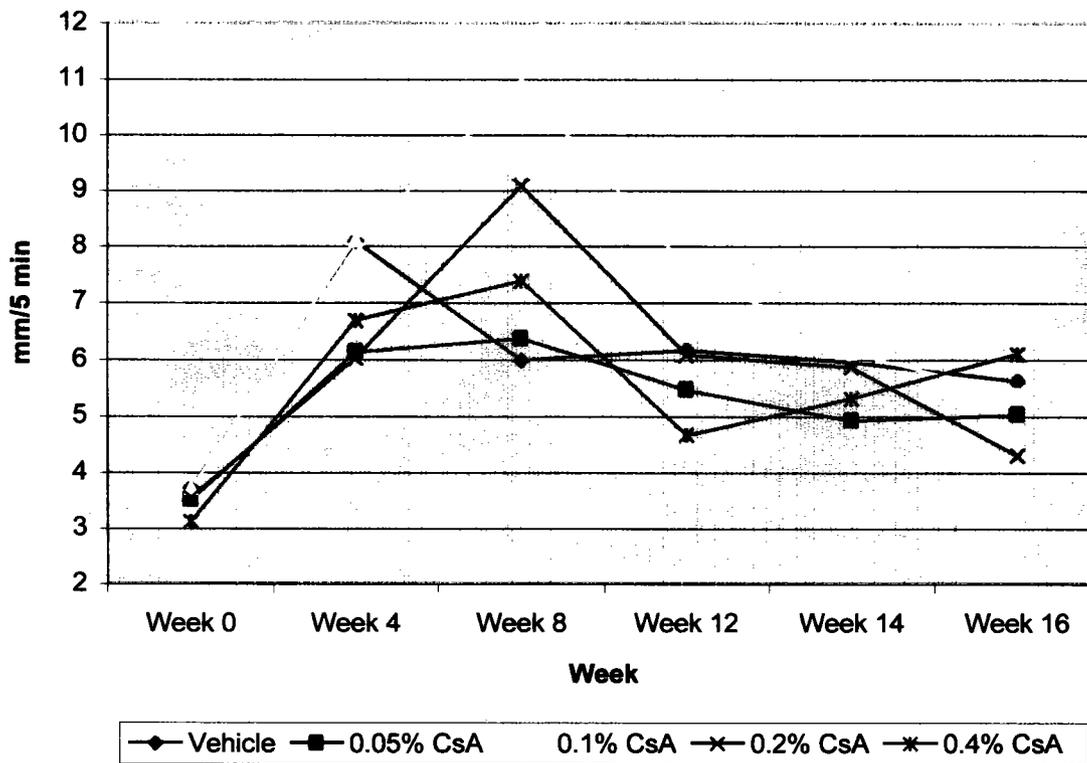
SPK – Corneal Staining

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline in each treatment group at each visit.

There are no statistically significant among-group differences.

Schirmer Values w/o Anesthesia



Reviewer's Comments

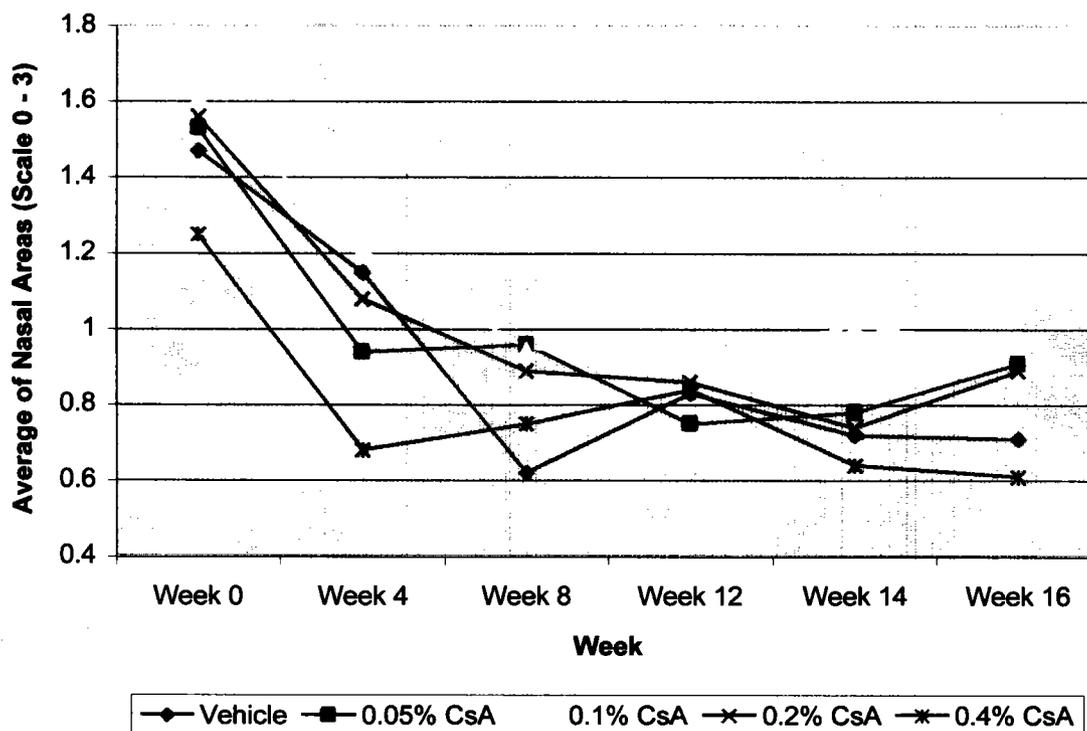
Schirmer Values w/o Anesthesia

A positive change from baseline indicates improvement.

There are statistically significant improvements from baseline at weeks 4 and 8 for the 0.1% cyclosporine treatment group.

There are no statistically significant among-group differences.

Nasal Rose Bengal Conjunctival Staining



Reviewer's Comments:

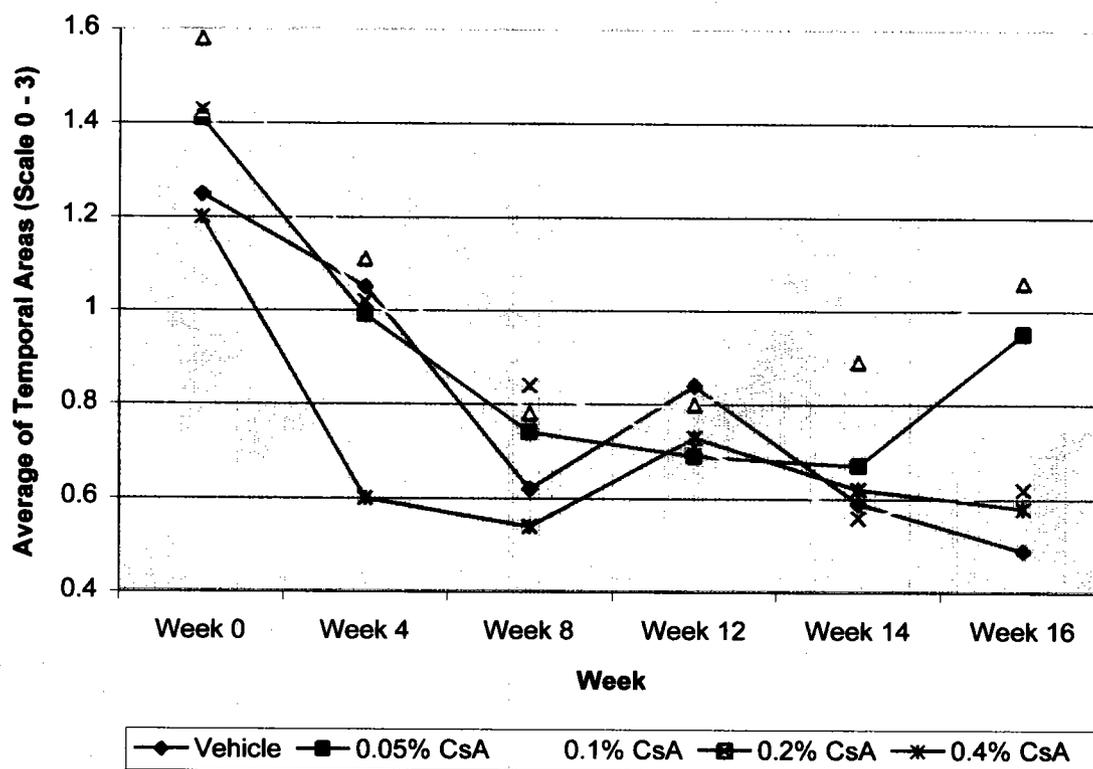
Nasal Rose Bengal Staining

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline in the 0.05%, and 0.2% cyclosporine groups at weeks 4, 8, and 12.

There are no statistically significant among-group differences.

Temporal Rose Bengal Conjunctival Staining



Reviewer's Comments:

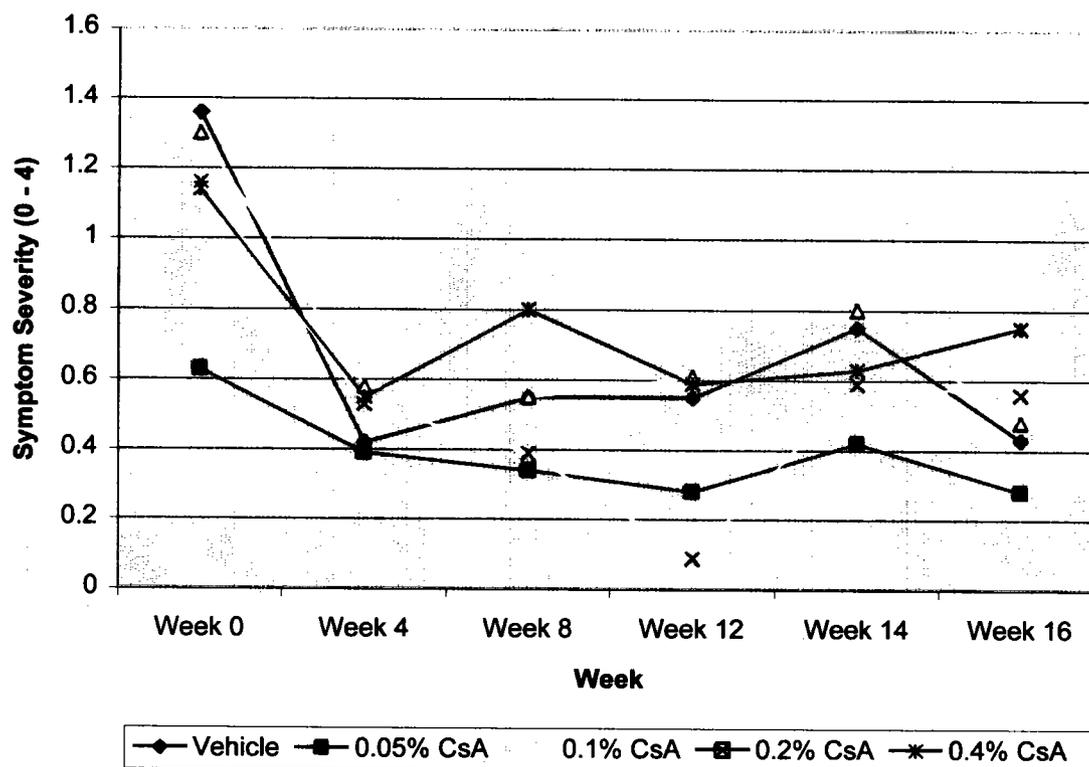
Temporal Rose Bengal Staining

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline in the 0.05% and 0.1 % cyclosporine groups at weeks 8 and 12.

There are no statistically significant among-group differences.

**Symptoms of Ocular Discomfort - Foreign Body Sensation
(Scheduled Visit Query)**



Reviewer's Comments:

Symptoms of Ocular Discomfort – Foreign Body Sensation (Scheduled Visit Query)

A negative change from baseline indicates improvement.

There are statistically significant improvements from baseline in the vehicle, 0.05%, 0.1%, and 0.2% cyclosporine groups at weeks 4, 8, and 12.

There is a statistically significant among-group difference at week 12, favoring 0.02% cyclosporine over 0.05% cyclosporine ($p = 0.046$) and at week 16, favoring vehicle over 0.05% and 0.4% cyclosporine ($p = 0.049$).

Other Symptoms of Ocular Discomfort

There are no other statistically significant among-group differences in the scheduled queries or diaries for dryness, burning/stinging, sandiness/grittiness, pain, itching, photophobia, blurred vision, tearing, or discharge.

Secondary Efficacy Measures**Tear Breakup Time**

Reviewer's Comments:

TBUT is similar across groups at baseline, and shows very slight improvement in most treatment groups (including vehicle) at Week 16. Statistical significance was not reported for this variable.

Other Secondary Efficacy Measures

There are no statistically significant among-group differences found in 1) tear film debris, 2) rose bengal staining, 3) brush cytology, 4) tear meniscus, 5) meibomian gland plugging or 6) the Ocular Surface Disease Index.

The Treatment Success efficacy variable cannot be evaluated easily because only five out of nine investigators performed this evaluation correctly

Tear protein data is not reliably interpretable because of problems with shipping delays and variations in collection techniques.

8.1.4 Safety Criteria

Vital Signs and Visual Acuity

There are no remarkable changes or differences in the vital signs of the cyclosporine groups versus the vehicle control group. Both had almost identical occurrences of pulse greater than 10 bpm above baseline at weeks 12 and 16 and at unscheduled visits. Both groups also had similar occurrences of systolic blood pressure greater than 20 mmHg above baseline at weeks 12 and 16. Diastolic blood pressure elevations 10 mmHg from baseline measured at weeks 12 and 16 in the cyclosporine groups ranged from two reports (0.05%) to eleven (0.1%). The vehicle group had four reports.

Cyclosporine groups and vehicle group had similar numbers of small and unremarkable changes (increases and decreases) in visual acuity.

IOP

Table 22

IOP: Listing of Patients with a Greater than 5 mmHg Increase from Baseline

There were generally no statistically significant differences in change from baseline IOP.

Biomicroscopy

Biomicroscopy examination for _____

_____ no clinically or statistically significant findings, either within groups or among groups at any treatment visits (except at week 8, where the vehicle group showed a statistically significant increase from baseline in erythema $p=0.016$).

Reviewer's Comments:

There are no clinically significant among-group differences in vital signs and visual acuity, IOP, or biomicroscopy.

Conjunctival Microbiology

Conjunctival cultures were performed at four of the study centers for 74 patients (about 14 or 15 per treatment group). The cyclosporine groups generally had fewer ocular microorganisms than did the vehicle group. Although there were changes in microbial flora in all patients from baseline to week 12, these changes were comparable among the groups. There did not appear to be a trend for overgrowth of ocular microorganisms with any of the treatments. No ocular infections occurred in any of the cyclosporine groups during treatment and post-treatment periods.

Conjunctiva from the 74 patients was cultured at baseline, week 12, and week 16. Baseline culture results were not reported for 8 patients, thus microbiology results were only recorded for 66 patients. Only 32/66 of the patients were culture positive at the baseline visit.

Only patients with baseline culture results and at least one follow-up culture report were analyzed. *Staphylococcus epidermidis* was the organism most frequently isolated from the conjunctiva of the dry eye patients in this study. There was a trend for fewer bacterial species and total strains of organisms recovered from the conjunctival cultures after cyclosporine treatment (week 12) than found prior to study treatment (week 0).

Reviewer's Comments:

No ocular infections occurred in any of the cyclosporine treatment groups during treatment and post-treatment periods. There were changes in microbial flora over the 12 weeks, but these changes were comparable across all groups, including vehicle.

CBC and Blood Chemistry

No patients experienced adverse events related to blood chemistry or hematology parameters, which included liver (GGT, SGPT, and SGOT) and renal (BUN, Cr., and uric acid) function tests. Both high and low values were reported, and the majority of patients with such lab data had a documented medical history which explained the abnormal findings.

Table 23
Blood Chemistry and Hematology Alert Values

Whole Blood Cyclosporine Concentrations

In most of the approximately 120 subjects administered topical cyclosporine from 0.05% to 0.4%, the trough whole blood concentrations of cyclosporine-A were less than 0.1 ng/ml over the 12 week dosing period. Only 5 subjects showed quantifiable trough cyclosporine-A concentrations of 0.102-0.157 ng/ml.

Comparison of trough whole blood cyclosporine-A concentrations for weeks _____ suggests no substantial accumulation following multiple ocular dosing for 12 weeks.

Peak whole blood concentration ($C_{\max 1-4h}$) of cyclosporine ranged from less than 0.1 ng/ml to 0.158 ng/ml. Average maximum whole blood concentrations of cyclosporine (C_{\max}) were less than 0.2 ng/ml.

Adverse Events Monitoring

Table 24
Adverse Events Regardless of Causality

The most frequently reported ocular adverse events were a feeling of ocular burning and SPK. The most frequently reported systemic adverse events among all treatment groups were bronchitis (three reports), and two reports each of depression, diarrhea, URI, and systemic infection (one sinus and one intestinal infection).

8.1.4 Reviewer's Summary of Efficacy and Safety:

This dose ranging study in a limited number of subjects demonstrates that the efficacy of cyclosporine is not dose related. No additional benefit in efficacy is evident with 0.2% and 0.4% cyclosporine concentrations. There are statistically significant improvements from baseline in the treatment groups (intent-to-treat population) favoring cyclosporine over vehicle in the selected efficacy measures.

Adverse experiences appear mostly limited to mild or moderate ocular events. There are no clinically significant differences in the safety variables recorded.

9 Overview of Efficacy

Study #	Protocol	Objective Signs Reaching Among-Group Statistical Significance	Subjective Symptoms Reaching Among-Group Statistical Significance
1	192731-002 Phase 3	Corneal Staining	Blurred Vision
			Refresh Use
			Sensitivity to Light
			Itching
			Composite Symptom Score
			Ocular Surface Disease Index
			Facial Expression Subjective Scale
			Investigator's Global Response to Treatment
2	192731-003 Phase 3	Categorized Schirmer with Anesthesia	Investigator's Global Response to Treatment
3	192731-001 Phase 2	None	Symptoms of Ocular Discomfort - Foreign Body Sensation

Study # 1 demonstrates one objective sign and eight subjective symptoms reaching among-group statistical significance.

Study # 2 demonstrates one objective sign and one subjective symptom reaching among-group statistical significance. The subjective symptom that demonstrates statistical significance (Global Response to Treatment) appears to have been evaluated differently by different investigators. Some investigators rated global response based on their clinical evaluations of the patients while other investigators queried their patients directly about their response to treatment.

Study #3 demonstrates one subjective symptom reaching among-group statistical significance.

The sponsor postulates that the greater vehicle effect in Study # 2 (Protocol 192731-003) made it difficult to show among-group differences in the intent-to-treat population. There are numerous statistically significant improvements from baseline seen in all treatment groups (pages 47 through 54).

Of note, there are several subjective symptoms that approach among-group significance at month 6 in Study # 2 (page 61). This may indicate that the maximum efficacy of the cyclosporine emulsion may not be obtained until after 6 months of treatment. Efficacy data from the extension phases of Studies 1 and 2 have not been submitted to the NDA to date.

Responder analysis

shows among-group statistical significance in both Studies # 1 and # 2.

Although both Phase 3 studies technically satisfy the criteria for efficacy of cyclosporine emulsion as set forth in their protocols (statistically significant differences between the active ingredient and vehicle for at least 1 objective sign and 1 subjective symptom), it is apparent that the studies did not replicate themselves.

10 Overview of Safety

There are no increases in the rate of ocular or systemic infections in the cyclosporine treatment groups. Adverse experiences appear mostly limited to mild and moderate ocular events in all three studies.

There were changes in the conjunctival microbial flora over 12 weeks in Study # 3, but these changes were comparable across all groups, including vehicle.

No patients experienced adverse events related to blood chemistry or hematology parameters (including liver and renal function tests) in the Phase 2 study.

OPHTHALMIC DRUGS
SUBCOMMITTEE

JULY 21, 1999

CYCLOSPORINE NDA 21023

PROPOSED LABELING
REDACTED

12 Conclusions

The submitted studies in NDA 21-023 evaluate the safety and efficacy of topical cyclosporine emulsion for the treatment of moderate to severe keratoconjunctivitis sicca.

13 Recommendations

Recommend NDA 21-023 be referred to the Ophthalmic Drugs Subcommittee of the Dermatologic and Ophthalmic Drugs Advisory Committee for discussion of the treatment of moderate to severe keratoconjunctivitis sicca. Following this Subcommittee meeting and the resolution of any chemistry/manufacturing issues and labeling issues, a decision will be made regarding the approval of NDA 21-023 for the treatment of moderate to severe keratoconjunctivitis sicca.

William M. Boyd, M.D.
Medical Officer

NDA 21-023
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers
HFD-725/Stat/LuHo
HFD-805/Micro/Riley
HFD-550/Chem/Tso
HFD-550/PM/Gorski
HFD-340/Carraras
HFD-550/PharmTox/Mukherjee