

OPHTHALMIC DRUGS  
SUBCOMMITTEE

JULY 21, 1999

CYCLOSPORINE NDA 21023

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APPENDIX 1

HISTOLOGICAL PHOTOGRAPHS

*REDACTED*

OPHTHALMIC DRUGS  
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APPENDIX 2  
PROPOSED LABELING  
(REDACTED)

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APPENDIX 3

DEFINITIONS OF RESPONDER  
AND PATIENTS WITH SJOGREN'S  
SYNDROME, SAMPLE SIZE  
DETERMINATION, AND  
SELECTION OF WORSE EYE

REDACTED

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OCULAR SURFACE DISEASE  
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APPENDIX 4 – RESULTS FOR ORIGINAL PRIMARY ENDPOINTS: SUM OF CORNEAL AND INTERPALPEBRAL CONJUNCTIVAL STAINING AND OCULAR SURFACE DISEASE INDEX<sup>®</sup> AND SCALES USED FOR EFFICACY VARIABLES

**Results for Original Primary Endpoints: Sum of Corneal and Interpalpebral Conjunctival Staining and Ocular Surface Disease Index**

The sum of corneal and interpalpebral conjunctival staining is summarized for each of the Phase 3 studies in the following table:

**Appendix 4, Table 1 Sum of Corneal and Interpalpebral Conjunctival Staining Phase 3 Studies (Intent-to-Treat Population)**

	Study 192371-002				Study 192371-003			
	CsA 0.05% N=135 <sup>a</sup>	CsA 0.1% N=134 <sup>a</sup>	Vehicle N=136 <sup>a</sup>	P value <sup>b</sup>	CsA 0.05% N=158 <sup>a</sup>	CsA 0.1% N=158 <sup>a</sup>	Vehicle N=156 <sup>a</sup>	P value <sup>b</sup>
Day 0	7.42 ± 2.12	7.44 ± 2.39	7.24 ± 2.23	0.635	7.46 ± 2.56	7.40 ± 2.33	7.27 ± 2.23	0.729
Change from baseline <sup>c</sup> :								
Month 1	-1.42 ± 2.10	-1.08 ± 1.73	-0.83 ± 1.91	0.104	-1.77 ± 1.87	-1.71 ± 2.22	-1.60 ± 2.18	0.578
Month 3	-1.55 ± 2.21	-1.40 ± 2.13	-1.21 ± 1.95	0.635	-1.64 ± 1.95	-1.99 ± 2.32	-1.63 ± 2.17	0.298
Month 4	-1.91 ± 2.19	-1.61 ± 2.41	-1.23 ± 2.09	0.050 <sup>d</sup>	-1.81 ± 2.04	-2.09 ± 2.41	-1.82 ± 2.57	0.559
Month 6	-2.52 ± 2.12	-2.13 ± 2.35	-1.77 ± 2.29	0.044 <sup>d</sup>	-2.22 ± 2.13	-2.17 ± 2.47	-2.33 ± 2.40	0.828

Note: CsA = cyclosporine ophthalmic emulsion. Values shown are mean ± standard deviation. Based on a 16-point severity scale (grades 0 to 15) using the worse eye. A negative change indicates improvement.

a The number of patients at day 0; sample sizes decreased at subsequent visits.

b Among-group P values from analysis of variance.

c Within-group P values (from paired t-test) for change from baseline were significant (P < 0.001) for all treatment groups at all visits in both studies.

d Pairwise comparisons (from analysis of variance) favored 0.05% CsA vs vehicle (P = 0.013 at month 4 and P = 0.011 at month 6).

In both studies, there was statistically significant improvement from baseline within each treatment group at all follow-up visits. In study 002 at months 4 and 6, there was statistically significantly greater improvement from baseline with 0.05% cyclosporine emulsion than with vehicle.

Results for the OSDI<sup>®</sup> is summarized for each of the Phase 3 studies in the following table:

**Appendix 4, Table 2 Ocular Surface Disease Index in Phase 3 Studies (Intent-to-Treat Population)**

	Study 192371-002				Study 192371-003			
	CsA 0.05% N=135 <sup>a</sup>	CsA 0.1% N=134 <sup>a</sup>	Vehicle N=136 <sup>a</sup>	P value <sup>b</sup>	CsA 0.05% N=158 <sup>a</sup>	CsA 0.1% N=158 <sup>a</sup>	Vehicle N=156 <sup>a</sup>	P value <sup>b</sup>
Day 0	0.44 ± 0.21	0.44 ± 0.21	0.43 ± 0.22	0.985	0.43 ± 0.21	0.41 ± 0.20	0.42 ± 0.20	0.860
Change from baseline <sup>c</sup> :								
Month 1	-0.06 ± 0.15	-0.05 ± 0.15	-0.03 ± 0.17	0.125	-0.04 ± 0.14	-0.05 ± 0.16	-0.06 ± 0.15	0.581
Month 3	-0.09 ± 0.18	-0.08 ± 0.19	-0.02 ± 0.19	0.046 <sup>d</sup>	-0.06 ± 0.16	-0.08 ± 0.16	-0.08 ± 0.17	0.514
Month 4	-0.10 ± 0.20	-0.08 ± 0.18	-0.04 ± 0.20	0.045 <sup>d</sup>	-0.05 ± 0.18	-0.07 ± 0.18	-0.07 ± 0.20	0.529
Month 6	-0.11 ± 0.20	-0.11 ± 0.19	-0.06 ± 0.20	0.069	-0.08 ± 0.16	-0.09 ± 0.17	-0.09 ± 0.20	0.876

Note: CsA = cyclosporine ophthalmic emulsion. Values shown are mean ± standard deviation. Based on a scale from 0 (no disability) to 1 (complete disability). A negative change indicates improvement.

- a The number of patients at day 0; sample sizes decreased at subsequent visits.
- b Among-group P values from analysis of variance.
- c Within-group P values (from paired t-test) for change from baseline were significant ( $P \leq 0.020$ ) for all treatment groups at all visits in both studies with the exception of study 002, vehicle group at months 1 and 3.
- d Pairwise comparisons (from analysis of variance) favored 0.05% CsA vs vehicle ( $P = 0.019$  at month 3 and  $P = 0.018$  at month 4).

In both studies, there was statistically significant improvement from baseline within each of the cyclosporine emulsion treatment groups at all follow-up visits. In study 002 at months 3 and 4, there was statistically significantly greater improvement from baseline with 0.05% cyclosporine emulsion than with vehicle.

**Scales Used for Efficacy Variables****Corneal and Conjunctival Staining**

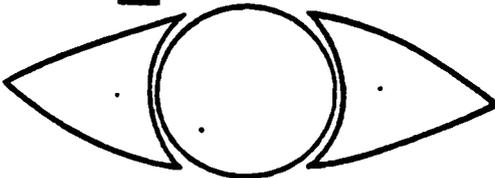
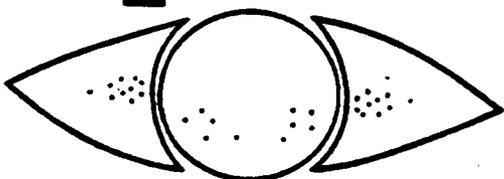
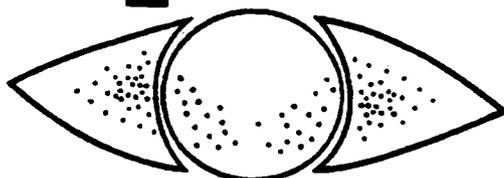
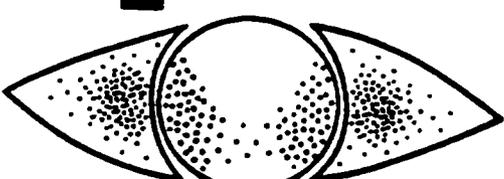
For corneal fluorescein staining, the entire cornea was evaluated using the yellow barrier filter and the slit lamp's cobalt blue illumination. For conjunctival staining, lissamine green was instilled and interpalpebral staining was evaluated only after 30 seconds, but before 2 minutes, had elapsed. Using white light of moderate intensity, the interpalpebral regions of the temporal and nasal conjunctiva were graded. Both corneal and conjunctival staining were evaluated using the Oxford Scheme 6-point scale of severity from grades 0 to 5, which is shown on the following page.

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For all staining variables, a negative change from baseline indicated improvement.

Oxford Scale

## GRADING OF CORNEAL AND CONJUNCTIVAL STAINING OXFORD SCHEME

<p><b>PICTURE A</b></p> 	<p><b>EQUAL TO OR LESS THAN PICTURE A</b></p>	<p><b>GRADE 0</b></p>
<p><b>PICTURE B</b></p> 	<p><b>MORE THAN IN PICTURE A, EQUAL TO OR LESS THAN IN PICTURE B</b></p>	<p><b>GRADE 1</b></p>
<p><b>PICTURE C</b></p> 	<p><b>MORE THAN IN PICTURE B, EQUAL TO OR LESS THAN IN PICTURE C</b></p>	<p><b>GRADE 2</b></p>
<p><b>PICTURE D</b></p> 	<p><b>MORE THAN IN PICTURE C, EQUAL TO OR LESS THAN IN PICTURE D</b></p>	<p><b>GRADE 3</b></p>
<p><b>PICTURE E</b></p> 	<p><b>MORE THAN IN PICTURE D, EQUAL TO OR LESS THAN IN PICTURE E</b></p>	<p><b>GRADE 4</b></p>
	<p><b>MORE THAN IN PICTURE E</b></p>	<p><b>GRADE 5</b></p>

Schirmer Tear Test

For the Schirmer tear test both with and without anesthesia, the amount of wetting was measured in millimeters (mm) using a graduated paper scale. Schirmer values were categorized using the following grades:

\_\_\_\_\_

A positive change from baseline indicated improvement.

OSDI<sup>®</sup> Score

To evaluate their functional disability from dry eye, patients completed the OSDI<sup>®</sup> questionnaire. \_\_\_\_\_

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### 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 as follows:

- 0 I do not have this symptom.
- 1 I seldom notice this symptom, but it does not make me uncomfortable.
- 2 I sometimes notice this symptom, it does make me uncomfortable, but it does not interfere with my activities.
- 3 I always notice this symptom, it does make me uncomfortable, but it does not interfere with my activities.
- 4 I always notice this symptom, it does make me uncomfortable, and it does interfere with my activities.

A negative change from baseline indicated improvement.

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APPENDIX 5

ADVERSE REACTIONS LEADING  
TO DISCONTINUATION

## APPENDIX 5 –ADVERSE EVENTS LEADING TO DISCONTINUATION

Table 1 shows the total number of patients in the Phase 3 studies who reported any adverse events that led to discontinuation of the study medication, summarized by body system.

**Appendix 5, Table 1 Number (%) of Patients in the Phase 3 Studies with Adverse Events that Led to Discontinuation of Study Drug by Body System<sup>a</sup>**

<b>COSTART Body System</b>	<b>0.05% Cyclosporine N=293</b>	<b>0.1% Cyclosporine N=292</b>	<b>Vehicle N=292</b>
Overall	21 (7.2%)	28 (9.6%)	19 (6.5%)
Body as a Whole	4 (1.4%)	4 (1.4%)	4 (1.4%)
Cardiovascular	4 (1.4%)	2 (0.7%)	3 (1.0%)
Digestive	3 (1.0%)	1 (0.3%)	1 (0.3%)
Endocrine	0 (0.0%)	1 (0.3%)	0 (0.0%)
Hemic and Lymphatic	1 (0.3%)	2 (0.7%)	0 (0.0%)
Metabolic and Nutritional	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nervous	0 (0.0%)	0 (0.0%)	1 (0.3%)
Respiratory	2 (0.7%)	5 (1.7%)	3 (1.0%)
Skin and Appendages	2 (0.7%)	1 (0.3%)	1 (0.3%)
Urogenital	1 (0.3%)	2 (0.7%)	2 (0.7%)
Special Senses	14 (4.8%)	19 (6.5%)	10 (3.4%)

<sup>a</sup> Patients may have had more than 1 adverse event at the time study drug was discontinued.

Table 2 shows the number of patients in the Phase 3 studies who reported ocular adverse events that led to discontinuation of the study medication.

**Appendix 5, Table 2 Number (%) of Patients in the Phase 3 Studies with Ocular Adverse Events that Led to Discontinuation of Study Drug<sup>a</sup>**

Preferred Term	0.05% Cyclosporine N=293	0.1% Cyclosporine N=292	Vehicle N=292
Overall	14 (4.8%)	19 (6.5%)	10 (3.4%)
burning eye	5 (1.7%)	7 (2.4%)	5 (1.7%)
foreign body sensation	3 (1.0%)	0 (0.0%)	1 (0.3%)
cataract (NOS)	2 (0.7%)	0 (0.0%)	0 (0.0%)
hyperemia conjunctival	2 (0.7%)	3 (1.0%)	0 (0.0%)
photophobia	2 (0.7%)	2 (0.7%)	0 (0.0%)
pruritus eye	2 (0.7%)	1 (0.3%)	0 (0.0%)
corneal ero	1 (0.3%)	0 (0.0%)	0 (0.0%)
discharge eye	1 (0.3%)	2 (0.7%)	0 (0.0%)
dry eye	1 (0.3%)	0 (0.0%)	1 (0.3%)
irritation eye	1 (0.3%)	2 (0.7%)	0 (0.0%)
pain eye	1 (0.3%)	3 (1.0%)	1 (0.3%)
pruritus eyelid	1 (0.3%)	0 (0.0%)	0 (0.0%)
asthenopia	0 (0.0%)	1 (0.3%)	0 (0.0%)
blepharitis	0 (0.0%)	0 (0.0%)	1 (0.3%)
conjunctivitis allergic	0 (0.0%)	0 (0.0%)	1 (0.3%)
conjunctivitis blepharo	0 (0.0%)	1 (0.3%)	0 (0.0%)
corneal abrasion	0 (0.0%)	1 (0.3%)	0 (0.0%)
epiphora	0 (0.0%)	3 (1.0%)	0 (0.0%)
erythema eyelid	0 (0.0%)	1 (0.3%)	0 (0.0%)
infect eye	0 (0.0%)	0 (0.0%)	1 (0.3%)
KCS	0 (0.0%)	1 (0.3%)	0 (0.0%)
scleritis	0 (0.0%)	0 (0.0%)	1 (0.3%)
stinging eye	0 (0.0%)	0 (0.0%)	1 (0.3%)
uveitis	0 (0.0%)	0 (0.0%)	1 (0.3%)
visual disturbance	0 (0.0%)	2 (0.7%)	1 (0.3%)

<sup>a</sup> Patients may have had more than 1 adverse event at the time study drug was discontinued.