CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-023

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA21-023
Name of Drug: Cyclosporine
Applicant: Allergan
Indication: Treatment of Moderate to Severe Keratoconjunctivitis Sicca
Documents Reviewed: Statistical Section (Vol.90-Vol.113) of NDA21-023
Dated 2/25/99 by CDER
Reviewer: Laura Lu, Ph.D.
Date of Review: 5/11/99

1. Introduction

NDA21-023 has been submitted for approval of cyclosporine 0.05% and 0.1% ophthalmic emulsions for treatment of moderate to severe keratoconjunctivitis sicca (KCS). This review will focus on the two pivotal phase III trials: Study 192371-002 and Study 192371-003.

2. Study 192371-002

2.1 Protocol

This study was a randomized, multi-center, double masked, parallel group, 6 months study for the comparison of the efficacy and safety of two cyclosporine treatment groups (0.05% and 0.1% ophthalmic emulsions) and one vehicle group.

The primary efficacy variables in this trial were **sum of corneal and interpalpebral conjunctival staining** (scale, 0-15) and **ocular surface disease index (OSDI)** (a continuous variable). The secondary efficacy variables are **facial expression subjective scale** (scale 1-5), **symptoms of dry eye** (scale 0-4), **Schirmer tear test** (with and without anesthesia, scale 1-5), **tear break-up time** (a continuous variable), **global evaluation of response to treatment** (investigator's evaluation, scale 0-6), **treatment success** (binary, 0-1), **use of Refresh** (a continuous variable), and **responder rate** (binary, 0-1).

Assuming that 30% of enrolled patients would be discontinued, a total of 420 patients were needed to obtain an estimated 300 evaluable patients at 6 months. Given an expected sample size of 100 per group, the power to detect a 3-grade difference between treatment groups in the change from baseline for the sum of corneal and interpalpebral conjunctival staining was greater than 0.86, using a 2-sided Wilcoxon rank-sum test with an estimated standard deviation of 6.49.

Patients who entered the masked treatment phase were asked to apply the received medicine twice daily. [redacted]. Patients were

evaluated at [redacted] patients would enter an extended treatment phase of 6 months. The data from the extended study were not included in this NDA.

"Worse eye" was used for all efficacy variables. **Categorical variables**, such as Schirmer values and symptoms, were analyzed by the Cochran-Mantel-Haenszel (CMH) procedure with modified ridits and stratified by investigator, or by other rank methods, as appropriate. **Continuous variables**, such as OSDI and the sum of corneal and interpalpebral conjunctival staining were analyzed with analysis of variance with treatment and sites as factors. For each variable, if a difference between the three treatment groups was found, three pairwise comparison was performed.

2.2 Sponsor's Report

2.2.a Patient disposition

A total of 405 patients (135 in 0.05% cyclosporine, 134 in 0.1% cyclosporine, and 136 in vehicle) enrolled in the masked treatment phase. In the intent-to-treat population, 75.6% (306/405) of the patients completed the entire treatment phase, and 24.4% (99/405) of the patients discontinued prematurely. Patients disposition in each treatment groups is summarized in the following table.

	0.05% cyclosporine	0.1% cyclosporine	Vehicle	Overall
Enrolled	135	134	136	405
Completer	107(79.3%)	103(76.9%)	96(70.6%)	306(75.6%)
Dropouts	28(20.7%)	31(23.1%)	40(29.4%)	99(24.4%)
Reasons for Discontinuation				
Lack of Efficacy	0(0.0%)	0(0.0%)	2(1.5%)	2(0.5%)
Adverse Event	9(6.7%)	15(11.2%)	6(4.4%)	30(7.4%)
Other	19(14.0%)	16(11.9%)	32(23.5%)	67(16.5%)

2.2.b Demographics

The 3 treatment groups were balanced with respect to age, sex, race, iris color, weight, and height (see Table 1 in Appendix A).

2.2.c Efficacy Results

The following results are based on ITT analysis with last observation carried forward. The mean values for each variables included in the parentheses are of the changes from baseline.

Primary efficacy variables:

- **Sum of corneal and interpalpebral conjunctival staining** showed significant between group differences at Months 4 and 6, at both visits favoring 0.05% cyclosporine vs

vehicle (-1.91 vs -1.23, P = 0.013 at Month 4 and -2.52 vs -1.77, P = 0.011 at Month 6). The detailed result is in Table 2 in Appendix A and Figure 1 in Appendix B.

• **OSDI** score showed significant among group differences at Months 3 and 4. At Months 3 and 4, the differences favored 0.05% cyclosporine vs vehicle (-0.09 vs -0.02, P = 0.019 at Month 3 and -0.10 vs -0.04, P = 0.018 at Month 4). The detailed result is in Table 3 in Appendix A and Figure 2 in Appendix B.

Secondary efficacy variables:

• **Facial expression subjective rating scale** showed significant among group differences at Months 3 and 6, favoring 0.05% cyclosporine vs vehicle at Month 3 (-0.47 vs -0.15, P = 0.021) and 0.1% cyclosporine vs vehicle at both visits (-0.52 vs -0.15, P = 0.010 at Month 3 and -0.85 vs -0.45, P = 0.011 at Month 6).

• **Composite symptom score of dry eye** showed significant among group differences at Months 3 and 6, at both visits favoring 0.05% cyclosporine vs vehicle (-2.44 vs -0.98, P = 0.008 at Month 3 and -3.32 vs -1.83, P = 0.029 at Month 6) and 0.1% cyclosporine vs vehicle (-2.28 vs -0.98, P = 0.042 at Month 3 and -4.03 vs -1.83, P = 0.003 at Month 6).

• **Investigator's evaluation of global response to treatment** showed significant among group differences at Months 4 and 6, favoring 0.05% cyclosporine vs vehicle at Month 6 (P=0.024), and 0.1% cyclosporine vs vehicle at Months 4 and 6 (P = 0.014 and 0.027). At Month 6, 71.9% of the patients in the 0.05% cyclosporine group, 71.0% of the patients in the 0.1% group, and 58.7% of the patients in the vehicle group showed a response to treatment.

• **The responder analysis** based [redacted] showed a significant among group difference at Month 6, favoring 0.05% cyclosporine vs vehicle (P=0.005) and approaching statistical significance for 0.1% cyclosporine vs vehicle (P = 0.053). At Month 6, responders comprised 50.0%, 44.2%, and 31.2% of patients in the 0.05% cyclosporine, 0.1% cyclosporine, and vehicle groups, respectively.

• **Average daily Refresh use** showed significant among group differences at Month 3 favoring 0.05% cyclosporine vs vehicle (-1.94 vs 0.25, P=0.017).

No significant among-group differences were found in the intent-to-treat analysis for **Schirmer values with or without anesthesia, days without Refresh use** and **treatment success.**

Per Protocol Analysis

The result of per protocol analysis was numerically (mean and standard deviation) similar to that of the ITT analysis in primary variables, but no statistically significant difference was shown due to a smaller sample size.

Subgroup Analysis

Analyses were performed for the following subgroups: severe disease, Sjögren's syndrome, age, sex, race, and iris color. There were general similarities in trend between the intent-to-treat analysis and the subgroup analyses.

3. Study 192371-003

3.1 Protocol

Identical to that of Study 192371-002.

3.2 Sponsor's Report

3.2.a Patient Disposition

A total of 472 patients were enrolled (158 in 0.05% cyclosporine, 158 in 0.1% cyclosporine, and 156 in vehicle). In the intent-to-treat population, 77.3% (365/472) of the patients completed the vehicle-controlled masked treatment phase, and 22.7% (107/472) of the patients discontinued prematurely. The percentages of patients who completed were 81.0% (128/158) in the 0.05% cyclosporine group, 72.8% (115/158) in the 0.1% cyclosporine group, and 78.2% (122/156) in the vehicle group. Patients disposition in each treatment groups is summarized in the following table.

	0.05% cyclosporine	0.1% cyclosporine	Vehicle	Overall
Enrolled	158	158	156	472
Completer	128(81.0%)	115(72.8%)	122(78.2%)	365(77.3%)
Dropouts	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%)
Other	19(12.1%)	26(15.4%)	26(16.7%)	71(15.0%)

3.2.b. Demographics

The 3 treatment groups were balanced with respect to age, sex, race, iris color, weight, and height (see Table 4 in Appendix A).

3.2.c Efficacy Results

The following results are based on ITT analysis with last observation carried forward. The mean values for each variables included in the parentheses are of the changes from baseline.

Primary Efficacy Variable

No statistical significances between the treatment groups and vehicle were found in **sum of corneal and interpalpebral conjunctival staining** and **OSDI**. The detailed result is in Tables 5 and 6 in Appendix A, and Figures 3 and 4 in Appendix B.

Secondary Efficacy Variable

- The **responder analysis** based on [redacted] showed a statistically significant among-group difference at Month 6, favoring both 0.05% (P=.03) and 0.1% (P=.007) cyclosporine vs vehicle. At Month 6, responders comprised 42.6%, 46.2%, and 29.2% of patients in the 0.05% cyclosporine, 0.1% cyclosporine, and vehicle groups, respectively.
- Statistically significant among-group differences were found in **categorized Schirmer tear test with anesthesia** at Month 6, favoring both 0.05% cyclosporine vs. vehicle (0.36 vs. -0.18, P≤0.001) and 0.1% cyclosporine vs. vehicle (0.31 vs. –0.18, P=0.001).
- Statistically significant among-group differences were found in **the investigator's evaluation of global response to treatment** at Month 3, favoring 0.1% cyclosporine over 0.05% cyclosporine (P=0.018) and vehicle (P=0.025). By Month 6, 65.6% (99/151) of the patients in the 0.05% cyclosporine group, 64.2% (95/148) of the patients in the 0.1% cyclosporine group, and 66.7% (98/147) of the patients in the vehicle group showed a response to treatment.

No significant among-group differences were found in **facial expression subjective scale, symptoms of dry eye, Schirmer values without anesthesia, use of Refresh (days without Refresh use** and **average daily Refresh use)**, and **treatment success.**

Per Protocol Analysis

The result of per protocol analysis was numerically (mean and standard deviation) similar to that of the ITT analysis in primary variables without showing any statistically significant among group difference.

Subgroup Analysis

Analyses were performed for the following subgroups: severe disease, Sjögren's syndrome, age, sex, race, and iris color. There were general similarities in trend between the intent-to-treat analysis and the subgroup analyses.

4. **Reviewer's Comment**

1. Multiple time points (Months 1, 3, 4 and 6) were studied for efficacy variables in both Study 192371-002 and Study 192371-003. No multiplicity adjustment procedure was specified for the results of these time points. This makes the observed significant differences difficult to interpret. In the table below, for each study, the reviewer listed the endpoints at which either the cyclosporine .05% group or the cyclosporine .1% group

showed consistent benefit across time and a statistically significant result compared with vehicle at Month 6. The inconsistency of the results between the two studies is clearly shown in this table.

Endpoints	Study 192371-002		Study 192371-003	
	cyclosporine .05% vs. vehicle	cyclosporine .1% vs. vehicle	cyclosporine .05% vs. vehicle	Cyclosporine .1% vs. vehicle
Primary				
Sum of Corneal and Interpalpebral Conjunctival Staining	X			
Secondary				
Facial Expression Subjective Rating Scale		X		
Composite Symptom Score	X	X		
Investigator's Evaluation of Global Response to Treatment	X	X		
Responder Analysis	X	X	X	X
Schirmer Tear Test with Anesthesia			X	X

2. In Study 192371-002, while the difference between cyclosporine .05% and the vehicle was statistically significant in the sum of corneal and interpalpebral conjunctival staining at Month 6 (P= 0.011), the mean difference was 1.75, which was much less than the clinical significant difference 3 as specified in the protocol.

3. No dose-response relation was shown for the treatment groups in either study. In Study 192371-002, cyclosporine .05% is numerically better than cyclosporine .1% in most efficay variables. In Study 192371-003, no consistent result was seen for the comparison between cyclosporine .05% vs. cyclosporine .1%; at Month 6, vehicle was numerically better than the two dose groups in the sum of corneal and interpalpebral conjunctival staining and facial expression subjective rating scores, and was comparable to the two dose groups in OSDI and symptom severity.

5. Final Conclusion

Studies 192371-002 and 192371-003 did not provide adequate evidence for the efficacy of cyclosporine .1% and .05%. The results in these two studies were inconsistent (see Table on page 6). In Study 192371-003, no statistically significant difference was found in either primary endpoint (sum of corneal and interpalpebral conjunctival staining and OSDI) between any of the cyclosporine groups and vehicle. In Study 192371-002, although cyclosporine .05% showed statistically significant improvement over vehicle in both sum of corneal and interpalpebral conjunctival staining and OSDI at some time points, these results are difficult to interpret without any pre-specified multiplicity adjustment procedure, and whether the mean treatment differences between cyclosporine

.05% vs. vehicle for these two endpoints (1.75 for sum of corneal and interpalpebral conjunctival staining and 0.06-0.07 for OSDI) were clinically significant should also be considered.

/S/

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Concur:

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CC: NDA 21-023
HFD-550/Div Files
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HFD-550/MO/Chambers
HFD-550/Div. File
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Table 1. Study 192371-002: Demographics

Variable Analyzed	Statistic or Category	0.05% cyclosporine (N=135)	0.1% cyclosporine (N=134)	Vehicle (N=136)	Overall (N=405)	P-value [a]
Age (Years)	N	135	134	136	405	0.151
	Mean	58.3	59.2	60.5	59.3	
	SD	14.8	14.0	14.3	14.4	
	Min	22.8	21.6	24.7	21.6	
	Max	90.3	86.7	88.8	90.3	
	Median	60.6	58.6	60.9	60.0	
Group	<40	15 (11.1%)	9 (6.7%)	11 (8.1%)	35 (8.6%)	0.458
	40-64	66 (48.9%)	75 (56.0%)	64 (47.1%)	205 (50.6%)	
	>64	54 (40.0%)	50 (37.3%)	61 (44.9%)	165 (40.7%)	
Sex	Male	21 (15.6%)	31 (23.1%)	35 (25.7%)	87 (21.5%)	0.099
	Female	114 (84.4%)	103 (76.9%)	101 (74.3%)	318 (78.5%)	
Race	Caucasian	107 (79.3%)	103 (76.9%)	102 (75.0%)	312 (77.0%)	0.934
	Black	4 (3.0%)	7 (5.2%)	9 (6.6%)	20 (4.9%)	
	Asian	5 (3.7%)	5 (3.7%)	6 (4.4%)	16 (4.0%)	
	Hispanic	18 (13.3%)	19 (14.2%)	18 (13.2%)	55 (13.6%)	
	Other [b]	1 (0.7%)	0 (0.0%)	1 (0.7%)	2 (0.5%)	
Iris Color	Blue	41 (30.4%)	37 (27.6%)	45 (33.1%)	123 (30.4%)	0.184
	Brown	65 (48.1%)	64 (47.8%)	66 (48.5%)	195 (48.1%)	
	Green	7 (5.2%)	14 (10.4%)	3 (2.2%)	24 (5.9%)	
	Hazel	22 (16.3%)	18 (13.4%)	22 (16.2%)	62 (15.3%)	
	Other [c]	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.2%)	
Weight (Kg)	N	135	133	135	403	0.033
	Mean	68.6	69.3	73.4	70.4	
	SD	16.7	14.4	17.6	16.4	
	Min	38.1	43.1	40.4	38.1	
	Max	132.9	116.1	127.0	132.9	
	Median	63.5	68.0	68.9	68.0	
Height (cm)	N	135	133	135	403	0.240
	Mean	163.1	165.0	164.4	164.2	
	SD	8.4	8.2	8.1	8.3	
	Min	134.6	147.3	135.9	134.6	
	Max	188.0	188.0	185.4	188.0	
	Median	162.6	165.1	165.1	162.6	

[a] P-values for age, weight, and height are from Analysis of Variance.
P-values for sex, race, and iris color are from Fisher's Exact test.
[b] 'Other' races include POLYNESIAN, SAMOAN.
[c] 'Other' irides include GRAY.

Table 2.a
Study 192371-002: Baseline Sum of Corneal and Interpalpebral Conjunctival Staining [a]

		0.05% cyclosporine (N=135)	0.1% cyclosporine (N=134)	Vehicle (N=136)	Among Group P-value[b]
Day 0					
	N	135	134	136	0.635
	Mean	7.42	7.44	7.24	
	SD	2.12	2.39	2.23	
	Min				
	Max				
	Median	7.00	7.00	7.00	

[a] Sum of Corneal and Interpalpebral Conjunctival Staining on a 16-point severity scale (grades 0 to 15) using worse eye.
[b] Among-group p-values are from Analysis of Variance.

Table 2.b
Study 192371-002: Change from Baseline in Sum of Corneal and Interpalpebral Conjunctival Staining

		0.05% cyclosporine (N=135)	0.1% cyclosporine (N=134)	Vehicle (N=136)	Among Group P-value[a]
Month 1					
	N	125	118	121	0.104
	Mean	-1.42	-1.08	-0.83	
	SD	2.10	1.73	1.91	
	Min				
	Max				
	Median	-1.00	-1.00	-1.00	
Month 3					
	N	129	124	126	0.635
	Mean	-1.55	-1.40	-1.21	
	SD	2.21	2.13	1.95	
	Min				
	Max				
	Median	-1.00	-1.00	-1.00	
Month 4					
	N	129	124	126	0.050
	Mean	-1.91	-1.61	-1.23	
	SD	2.19	2.41	2.09	
	Min				
	Max				
	Median	-2.00	-2.00	-1.00	

Month 6				
	N	129	124	126	0.044
	Mean	-2.52	-2.13	-1.77	
	SD	2.12	2.35	2.29	
	Min				
	Max				
	Median	-3.00	-2.00	-2.00	

Table 2.c
Study 192371-002: P-values of Pairwise Comparison in Sum of Corneal and Interpalpebral Conjunctival Staining When among Group Comparison Is Significant [a]

	0.1% cyclosporine	Vehicle
Month 4		
0.05% cyclosporine	0.167	0.013
0.1% cyclosporine		0.323
Month 6		
0.05% cyclosporine	0.168	0.011
0.1% cyclosporine		0.290

[a] P-values are from Analysis of Variance.

Table 3.a
Study 192371-002: Baseline Ocular Surface Disease Index [a]

		0.05% cyclosporine (N=135)	0.1% cyclosporine (N=134)	Vehicle (N=136)	Among Group P-value[b]
Day 0					0.985
	N	135	134	136	
	Mean	0.44	0.44	0.43	
	SD	0.21	0.21	0.22	
	Min				
	Max				
	Median	0.40	0.41	0.40	

[a] OSDI on a 0 (no disability) to 1 (complete disability) scale.
[b] Among-group p-values are from Analysis of Variance.

Table 3.b
Study 192371-002: Change from Baseline in Ocular Surface Disease Index

		0.05% cyclosporine (N=135)	0.1% cyclosporine (N=134)	Vehicle (N=136)	Among Group P-value[b]
Month 1					0.125
	N	123	117	123	
	Mean	-0.06	-0.05	-0.03	
	SD	0.15	0.15	0.17	
	Min				
	Max				
	Median	-0.04	-0.05	-0.04	
Month 3					0.046
	N	128	124	127	
	Mean	-0.09	-0.08	-0.02	
	SD	0.18	0.19	0.19	
	Min				
	Max				
	Median	-0.08	-0.07	-0.04	
Month 4					0.045
	N	128	124	127	
	Mean	-0.10	-0.08	-0.04	
	SD	0.20	0.18	0.20	
	Min				
	Max				
	Median	-0.11	-0.08	-0.04	

Month 6				
	N	128	124	127	0.069
	Mean	-0.11	-0.11	-0.06	
	SD	0.20	0.19	0.20	
	Min				
	Max				
	Median	-0.08	-0.11	-0.06	

Table 3.c

Study 192371-002: P-values of Pairwise Comparison in Ocular Surface Disease Index When among Group Comparison Is Significant [a]

	0.1% cyclosporine	Vehicle
Month 3		
0.05% cyclosporine	0.681	0.019
0.1% cyclosporine		0.060
Month 4		
0.05% cyclosporine	0.431	0.018
0.1% cyclosporine		0.094

[a] P-values are from Analysis of Variance.

Table 4. Study 192371-003: Demographics

Variable Analyzed	Statistic or Category	0.05% cyclosporine (N=158)	0.1% cyclosporine (N=158)	Vehicle (N=156)	Overall (N=472)	P-value [a]
Age (Years)	N	158	158	156	472	0.416
	Mean	59.1	60.8	59.3	59.8	
	SD	13.2	12.7	14.3	13.4	
	Min	24.0	28.1	27.5	24.0	
	Max	86.5	89.0	90.3	90.3	
	Median	59.5	61.3	57.2	59.5	
Group	<40	10 (6.3%)	7 (4.4%)	16 (10.3%)	33 (7.0%)	0.253
	40-64	85 (53.8%)	78 (49.4%)	80 (51.3%)	243 (51.5%)	
	>64	63 (39.9%)	73 (46.2%)	60 (38.5%)	196 (41.5%)	
Sex	Male	28 (17.7%)	23 (14.6%)	24 (15.4%)	75 (15.9%)	0.742
	Female	130 (82.3%)	135 (85.4%)	132 (84.6%)	397 (84.1%)	
Race	Caucasian	146 (92.4%)	140 (88.6%)	142 (91.0%)	428 (90.7%)	0.447
	Black	4 (2.5%)	9 (5.7%)	6 (3.8%)	19 (4.0%)	
	Asian	3 (1.9%)	1 (0.6%)	0 (0.0%)	4 (0.8%)	
	Hispanic	5 (3.2%)	7 (4.4%)	8 (5.1%)	20 (4.2%)	
	Other [b]	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.2%)	
Iris Color	Blue	56 (35.4%)	58 (36.7%)	64 (41.0%)	178 (37.7%)	0.786
	Brown	61 (38.6%)	63 (39.9%)	50 (32.1%)	174 (36.9%)	
	Green	13 (8.2%)	12 (7.6%)	15 (9.6%)	40 (8.5%)	
	Black	0 (0.0%)	2 (1.3%)	0 (0.0%)	2 (0.4%)	
	Hazel	26 (16.5%)	20 (12.7%)	24 (15.4%)	70 (14.8%)	
	Other [c]	2 (1.3%)	3 (1.9%)	3 (1.9%)	8 (1.7%)	
Weight (Kg)	N	157	158	156	471	0.598
	Mean	69.2	69.8	70.7	69.9	
	SD	16.1	15.8	15.9	15.9	
	Min	38.1	45.4	46.3	38.1	
	Max	133.8	136.1	117.9	136.1	
	Median	66.7	69.6	67.1	68.0	
Height (cm)	N	157	158	156	471	0.660
	Mean	165.5	164.9	164.9	165.1	
	SD	9.0	10.4	9.5	9.6	
	Min	147.3	129.5	139.7	129.5	
	Max	195.6	193.0	195.6	195.6	
	Median	165.1	163.2	165.1	165.1	

[a] P-values for age, weight, and height are from Analysis of Variance.
P-values for sex, race, and iris color are from Fisher's Exact test.
[b] 'Other' races include GREEK.
[c] 'Other' irides include BLUE-GRAY, BLUE/GRAY, BROWNGRAY, GOLD, GRAY, GREY.

Table 5.a
Study 192371-003: Baseline Sum of Corneal and Interpalpebral Conjunctival Staining [a]

		0.05% cyclosporine (N=158)	0.1% cyclosporine (N=158)	Vehicle (N=156)	Among Group P-value[b]
Day 0					
	N	158	158	156	0.729
	Mean	7.46	7.40	7.27	
	SD	2.56	2.33	2.23	
	Min				
	Max				
	Median	7.00	7.00	7.00	

[a] Sum of Corneal and Interpalpebral Conjunctival Staining on a 16-point severity scale (grades 0 to 15) using worse eye.
[b] Among-group p-values are from Analysis of Variance.

Table 5.b
Study 192371-003: Change from Baseline in Sum of Corneal and Interpalpebral Conjunctival Staining

		0.05% cyclosporine (N=158)	0.1% cyclosporine (N=158)	Vehicle (N=156)	Among Group P-value[b]
Month 1					
	N	146	142	141	0.578
	Mean	-1.77	-1.71	-1.60	
	SD	1.87	2.22	2.18	
	Min				
	Max				
	Median	-2.00	-2.00	-2.00	
Month 3					
	N	151	150	146	0.298
	Mean	-1.64	-1.99	-1.63	
	SD	1.95	2.32	2.17	
	Min				
	Max				
	Median	-2.00	-2.00	-2.00	
Month 4					
	N	151	150	146	0.559
	Mean	-1.81	-2.09	-1.82	
	SD	2.04	2.41	2.57	
	Min				
	Max				
	Median	-2.00	-3.00	-2.00	

Month 6					
	N	152	150	146	0.828
	Mean	-2.22	-2.17	-2.33	
	SD	2.13	2.47	2.40	
	Min				
	Max				
	Median	-2.00	-2.00	-2.00	

APPEARS THIS WAY
ON ORIGINAL

Table 6.a
Study 192371-003: Baseline Ocular Surface Disease Index [a]

		0.05% cyclosporine (N=158)	0.1% cyclosporine (N=158)	Vehicle (N=156)	Among Group P-value[b]
Day 0					
	N	158	158	156	0.860
	Mean	0.43	0.41	0.42	
	SD	0.21	0.20	0.20	
	Min				
	Max				
	Median	0.38	0.37	0.39	

[a] OSDI on a 0 (no disability) to 1 (complete disability) scale.
[b] Among-group p-values are from Analysis of Variance.

Table 6.b
Study 192371-003: Change from Baseline in Ocular Surface Disease Index

		0.05% cyclosporine (N=158)	0.1% cyclosporine (N=158)	Vehicle (N=156)	Among Group P-value[b]
Month 1					
	N	147	141	141	0.581
	Mean	-0.04	-0.05	-0.06	
	SD	0.14	0.16	0.15	
	Min				
	Max				
	Median	-0.04	-0.04	-0.05	
Month 3					
	N	151	149	146	0.514
	Mean	-0.06	-0.08	-0.08	
	SD	0.16	0.16	0.17	
	Min				
	Max				
	Median	-0.06	-0.08	-0.07	
Month 4					
	N	151	149	146	0.529
	Mean	-0.05	-0.07	-0.07	
	SD	0.18	0.18	0.20	
	Min				
	Max				
	Median	-0.05	-0.06	-0.08	

Month 6					
	N	152	149	146	0.876
	Mean	-0.08	-0.09	-0.09	
	SD	0.16	0.17	0.20	
	Min				
	Max				
	Median	-0.07	-0.09	-0.09	

APPEARS THIS WAY
ON ORIGINAL

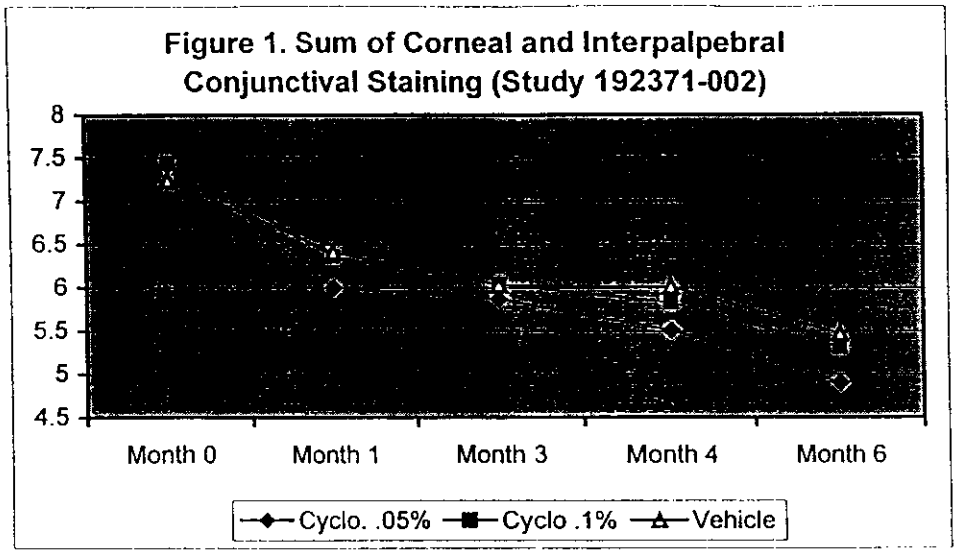
Figure 1. Sum of Corneal and Interpalpebral Conjunctival Staining (Study 192371-002)
8
7.5
7
6.5
6
5.5
5
4.5
Month 0
Month 1
Month 3
Month 4
Month 6
Cyclo. .05%
Cyclo .1%
Vehicle

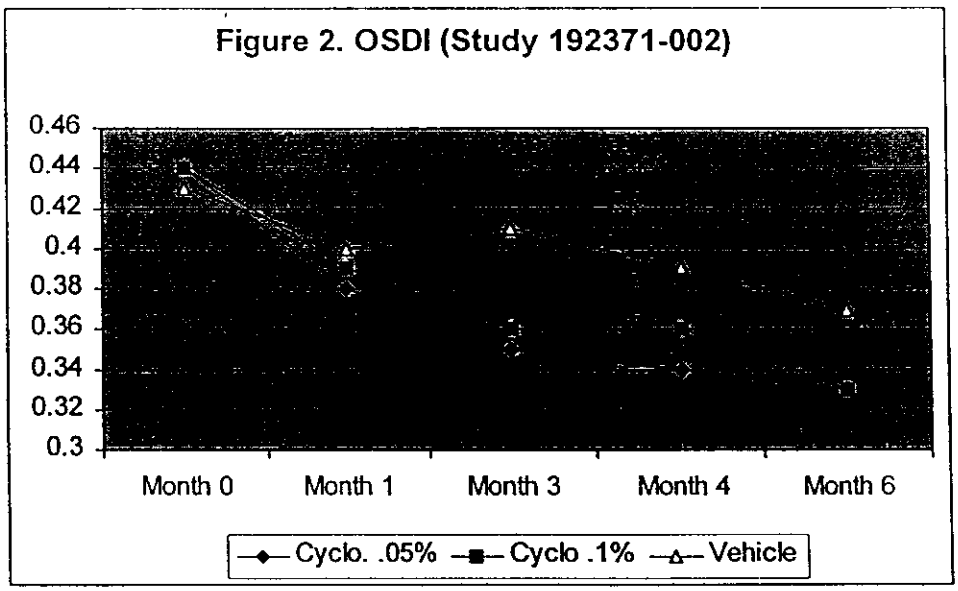
Figure 2. OSDI (Study 192371-002)
0.46
0.44
0.42
0.4
0.38
0.36
0.34
0.32
0.3
Month 0
Month 1
Month 3
Month 4
Month 6
Cyclo. .05%
Cyclo .1%
Vehicle

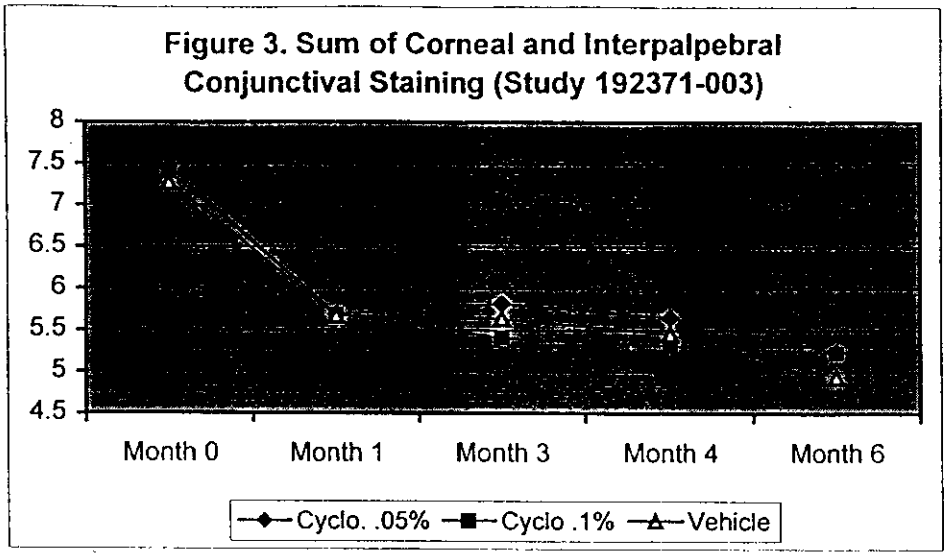
Figure 3. Sum of Corneal and Interpalpebral Conjunctival Staining (Study 192371-003)
8
7.5
7
6.5
6
5.5
5
4.5
Month 0
Month 1
Month 3
Month 4
Month 6
Cyclo. .05%
Cyclo .1%
Vehicle

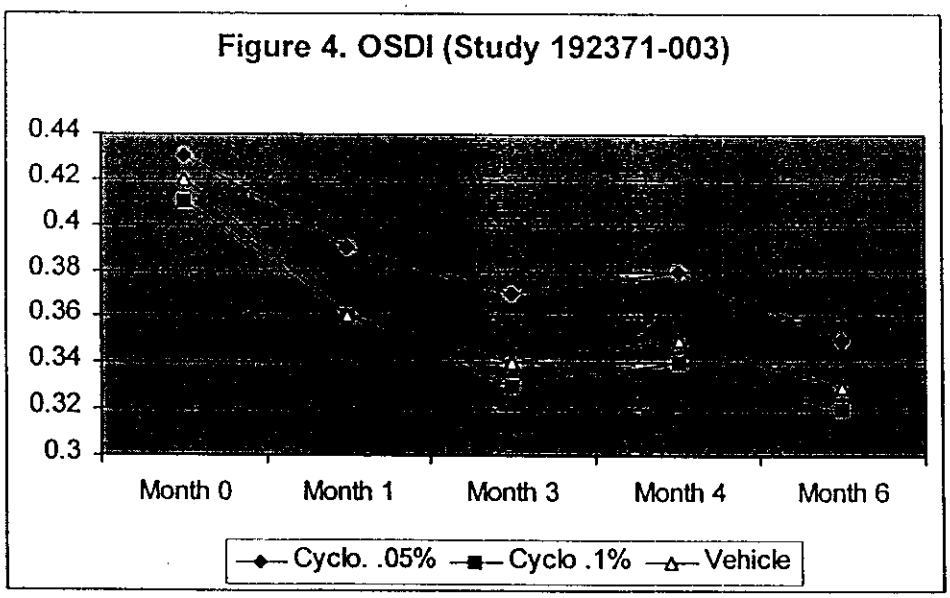
Figure 4. OSDI (Study 192371-003)
0.44
0.42
0.4
0.38
0.36
0.34
0.32
0.3
Month 0
Month 1
Month 3
Month 4
Month 6
Cyclo. .05%
Cyclo .1%
Vehicle

Statistical Review of NDA21-023 (Cyclosporine)
Amendment to original statistical review dated
6/30/99

1. On page 1, in the second paragraph under section 2.1 'Protocol', the last secondary variable 'responder rate' should be modified to 'OSDI responder rate'.
2. On page 6, one additional comment should be added under the 'Reviewer's Comment':
   '4. The responder analysis based on corneal staining, Schirmer with anesthesia, blurred vision, and Refresh was not pre-specified as a secondary endpoint in the original protocol. Therefore, this responder analysis is post hoc and the result is not interpretable in terms of statistical significance.

/S/

Laura Lu, Ph.D.
Mathematical Statistician

Concur: /S/

Stan Lin, Ph.D. 7/1/99
Team Leader

CC:
NDA21-023
HFD-550/MO/Boyd
HFD-550/PM/Gorski
HFD-550/MO/Chambers
HFD-550/Div. File
HFD-725/Lu
HFD-725/Lin S.
HFD-725/Huque
HFD-725/Div. File

Review Amendment

NDA21-023
Name of Drug: Cyclosporine
Applicant: Allergan
Indication:
Documents Reviewed: Volume 1 and 2 of Amendment of NDA21-023
Dated 12/09/99 by CDER
Reviewer: Laura Lu, Ph.D.
Date of Comment: 1/10/2000

In the newly submitted amendment, the Sponsor presented study data of a subpopulation of patients whose dry eye disease was inadequately controlled by tear substitute (Refresh). The FDA review statistician has the following comments regarding the subpopulation and the analysis results.

1. Since the sub-population was selected unblindedly after the original studies, the interpretability of the analysis result is questionable. Without a pre-specified clinical criteria, a subpopulation could be selected in numerous ways and it would not be surprising to find a subpopulation with significant results even when the drug is not effective. Also, there may not be a unique way in selecting patients. For example, the Sponsor's definition for 'patients whose dry eye disease was inadequately controlled by tear substitute' is
1). patients was using >4 unites/day of Refresh at baseline;
2). Schirmer tear test without anesthesia was ≤ 5 mm/5 min in at least 1 eye;
3). the sum of stainings was ≥ +2 in the same eye where Schirmer was ≤ 5 mm/5 min;
4). on the OSDI questionnaire, patients had a minimum baseline score and answered at least 9 of the 12 questions.
The uniqueness of these criteria in defining the subpopulation can be questioned by whether only or all the four endpoints should be used and whether the cut points are preferable to others, say, how about changing 9 questions to 8 questions in the last criteria? It is very difficult to assess statistical significance of a post-hoc subpopulation result.

2. Assume the clinical soundness of the subpopulation overcomes the issue raised in point 1, the statistical evidence of Sponsor's result is still not
Sponsor identified two endpoints (Categorized Schirmer Values with Anesthesia and Blurred Vision) with p-value < 0.05 in both studies by Fisher's LSD method. In Study 002, the p-values for between group comparisons were 0.04 and <0.001 for Categorized Schirmer Values with Anesthesia and .048 for Blurred Vision. In Study 003, the p-values for between group comparisons were <0.001 for Categorized Schirmer Values with Anesthesia and .019 for Blurred Vision. However, there were 5 subjective and 5 objective endpoints specified in the original NDA, and the p-values just mentioned were not adjusted for multiplicity. If Bonfferoni method is applied, the p-values for between group comparison were 0.2 and <0.005 for Categorized Schirmer Values with Anesthesia and were 0.24 and 0.1 for Blurred Vision in Study 002 and Study 003, respectively. So only

Categorized Schirmer Values with Anesthesia showed statistical significance (p-value<0.05) in Study 003.

LSL

Laura Lu, Ph.D.
Mathematical Statistician

Concur: LSL

Stan Lin, Ph.D. 2/14/00
Team Leader

CC:
NDA 21-003
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