CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-023

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-023
Amendment

NDA 21-023	**Submissions:**	December 20, 2002
Medical Officer's Review #9	**Review Completed:**	December 23, 2002

Proposed Tradename:	Restasis
Generic Name:	Cyclosporine ophthalmic emulsion, 0.05%
Sponsor:	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534
Pharmacologic Category:	immunomodulator
Proposed Indication:	[redacted]
Dosage Form and Route of Administration:	ophthalmic emulsion for topical ocular administration

Reviewer's Comments:

Revised labeling based on previous review, discussion with the applicant, discussion between ODEV and the Division, and a corrected package insert transmitted by the applicant on December 20, 2002.

The applicant proposes inserting the word "topical" before "anti-inflammatory" in the Clinical Evaluations *and* Indications and Usage *sections of the label.*

This is acceptable.

10 Draft Labeling Page(s) Withheld

Recommendations:

It is recommended that NDA 21-023 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Restasis (cyclosporine ophthalmic emulsion) 0.05% to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

There are no recommendations for additional postmarketing studies.

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/Chem TL/Ng
HFD-550/PM/Gorski
HFD-550/PharmTox/Mukherjee
HFD-550/Pharm Tox TL/Yang
HFD-880/ Biopharm TL/Bashaw

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Wiley Chambers
12/23/02 03:29:14 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-023
Amendment

NDA 21-023	**Submissions:**	September 7, 2001 April 23, 2002 June 17, 2002 July 11, 2002 September 6, 2002 November 15, 2002 December 16, 2002
Medical Officer's Review #8	**Review Completed:**	December 19, 2002
Proposed Tradename:	Restasis	
Generic Name:	Cyclosporine ophthalmic emulsion, 0.05%	
Sponsor:	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534	
Pharmacologic Category:	immunomodulator	
Proposed Indication:	[redacted]	
Dosage Form and Route of Administration:	ophthalmic emulsion for topical ocular administration	

Reviewer's Comments:

Revised labeling is based on further discussion within the Division on December 19, 2002, regarding the Clinical Pharmacology, Clinical Evaluations, *and* Indication and Usage *sections and subsections of the labeling.*

10 Draft Labeling Page(s) Withheld

Recommendations:

It is recommended that NDA 21-023 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Restasis (cyclosporine ophthalmic emulsion) 0.05%

There are no recommendations for additional postmarketing studies.

William M. Boyd, M.D.
Medical Officer

NDA 21-023
HFD-550/Div Files
HFD-550/MO/Boyd
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William Boyd
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Wiley Chambers
12/20/02 03:26:37 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-023
Amendment

NDA 21-023	**Submissions:** December 16, 2002
Medical Officer's Review #7	**Review Completed:** December 16, 2002

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: immunomodulator

Proposed Indication: [redacted]

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

Submitted:

Revised labeling based on previous review, discussion with the applicant, and a clean-corrected package insert transmitted by the applicant on 12/16/02.

Reviewer's Comments:

Two labeling comments appearing in the Chemist's review, dated 12/13/02 12:12:56 PM in DFS, were not included in the final drug product labeling.

1) Under Description, "The amount as [redacted] should replace 0.05% for cyclosporine."

The proportion of the active ingredient, cyclosporine, is acceptable per CFR 201.100 (b)(4).

2) Under How Supplied, "The word vial should be replaced by [redacted] as the latter is the description for a sealed container as per C-DRR-00907, Package Type, CDER Data Standards Manual."

Disagree. Per the CDER Data Standards manual, the proposed single-use LDPE container is a vial ("A container designed for use with parenteral drug products").

5 Draft Labeling Page(s) Withheld

Recommendations:

It is recommended that NDA 21-023 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Restasis (cyclosporine ophthalmic emulsion) 0.05%

There are no recommendations for additional postmarketing studies.

William M. Boyd, M.D.
Medical Officer

NDA 21-023
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William Boyd
12/16/02 02:33:44 PM
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Wiley Chambers
12/16/02 02:54:09 PM
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Medical Officer's Review of NDA 21-023
Office of Drug Safety Consultation

NDA 21-023	**Submission:**	December 11, 2002
Medical Officer's Review #6	**Review Completed:**	December 11, 2002

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: immunomodulator

Proposed Indication: [redacted]

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

Submitted:

Submitted is a Office of Drug Safety memorandum in response to a November 19, 2002 request from the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products for a re-review of the proprietary name, Restasis.

In response to a previous consultation to the Office of Post-Marketing Drug Risk Assessment (response received August 28, 2000), OPDRA stated it had no objections to the use of the proprietary name, Restasis. Recommendations for labeling revisions were made to minimize potential errors with the use of this product.

Office of Drug Safety Comments:

Based upon review of the revised package insert labeling, DMETS acknowledges that packaging the product in single-use containers and labeling them as single-use addresses the concern surrounding the [redacted] described in Appendix A (A.2.a. and A.2.b.). However, it appears that 0.4 mL is more than the amount needed for a single dose. The estimated volume required for two drops based on 15-20 drops per milliliter is 0.1 – 0.13 mL. Therefore, there is a risk that patients may save the vial and use the remaining drug in the interest of saving money. The risks of using the drug beyond the single dose needs to be clearly communicated to practitioners, patients and caregivers

especially since the product does not contain a preservative. Another way to minimize this risk is to use the least amount of overfill beyond the volume needed for two drops. Additionally, if space permits, we recommend that the terminology [redacted] be added to the labels and labeling.

Medical Officer's Comments:

Single-use, unpreserved topical ophthalmic drug products uniformly contain a volume exceeding the amount needed for a single dose (including overfill).

Because of the material properties of the LDPE vial, this additional volume assists the patient in administering the correct amount of drug product. The additional volume is also required for product stability.

With every single-use, unpreserved product there is the risk that patients may save the vial and use the remaining drug at a later time. The risks of using the cyclosporine ophthalmic emulsion single-use vial beyond the single dose is adequately communicated to practitioners, patients and caregivers within the Restasis package insert:

> The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.
>
> Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

The Restasis tray label is marked " [redacted] The [redacted] is marked ' [redacted] 'Both tray label and [redacted] indicate the drug product is [redacted]

Office of Drug Safety Comments:

Since the initial review, DMETS identified two additional proprietary names with potential for confusion with Restasis since we conducted our initial review. However, DMETS does not anticipate that these product names will cause confusion in the US marketplace at this time.

Medical Officer's Comments: *Agree.*

Office of Drug Safety Comments:

Regarding consultation Appendix A (Labeling, Packaging and Safety Related Issues from Initial ODS (OPDRA) Consult:

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/s/

Wiley Chambers
12/23/02 05:06:41 PM

We have safety concerns with the packaging of this product in a low-density polyethylene (LDPE) container. In particular, these concerns relate to the labeling that appears on the flange. This labeling should be clear and distinctive, since this type of packaging is being utilized in the manufacturing of other drug products. We also recommend that the [redacted], since the product will be loosely stored in bins within the institutional setting.

Some of the products that are packaged in a like fashion include nonprescription ophthalmic lubricants and are utilized by the same patient population. These products include the following: AquaSite, Bion Tears, Celluvisc, Hypo Tears PF, Preservative Free Moisture Eyes, Refresh, Refresh Plus, OcuCoat PF, and Tears Natural Free. The possibility exists for a patient or health care provider to confuse one product with the other. The patient would then receive an underdose or overdose of Restasis in the process.

Confusion between other non-ophthalmic products on the market in the U.S. that are packaged in LDPE containers has been documented in numerous reports to the FDA. These products are generally pulmonary inhalation solutions from various manufacturers and include the following generic substances: albuterol sulfate 0.083% inhalation solution, sodium chloride inhalation solution, and ipratropium bromide 0.02% inhalation solution. Although the volume of these products is generally larger (2.5 to 3 mL) than the single-use ophthalmic droppers proposed for Restasis (0.4 mL), it is possible that these products could be confused with Restasis, or vice versa.

Medical Officer's Comments:

The LDPE vial will be [redacted] with, [redacted]

The proposed labeling on the Restasis vial is clear and distinctive. The proposed packaging of the tray and physician sample carton is clear and distinctive.

Unlike the nonprescription ophthalmic lubricants packaged in a like fashion, Restasis is a white, opaque emulsion. There is no perceived additional risk to the indicated population from the use of a nonprescription ophthalmic lubricant. Based on the safety profile of Restasis, there is no perceived safety risk from the inadvertent use of Restasis in the population utilizing nonprescription ophthalmic lubricants.

The volume and packaging of non-ophthalmic products on the market in the U.S. is unlike the proposed packaging of the Restasis vial, carton, or tray. Again, the proposed labeling on the Restasis vial is clear and distinctive; the proposed packaging of the tray and physician sample carton is clear and distinctive.

The phrase " [redacted] " is quite restrictive and could be confusing to the user. Some clarification should be provided regarding the following issues.

How many doses or drops will each vial deliver? If more than two drops are deliverable, then the statement above seems to imply that [redacted] according to the statement above, if strictly adhered to by the user.

Medical Officer's Comments:

The phrase " [redacted] is no longer found in the package insert, Restasis vial, tray or [redacted] It has been replaced, where appropriate with " [redacted] or " [redacted] These phases are intentionally more restrictive than " [redacted]

In the interest of economy and conserving the drug product, it also seems likely that a patient be will inclined to use the remainder of the dropper, if the dosing is close to a 12-hour interval. Given the nature of cyclosporin (sic) therapy in an ophthalmic, preservative-free solution, can a local infection result from droppers used within, for example, 13 hours? Because the stated time to expiration of the product is the same as the dosing interval, significant confusion and misuse seem likely.

Medical Officer's Comments:

See previous comment regarding " [redacted] "

Again, with every single-use, unpreserved product there is the risk that patients may save the vial and use the remaining drug at a later time. The risks of using the cyclosporine ophthalmic emulsion single-use vial beyond the single dose is adequately communicated to practitioners, patients and caregivers within the Restasis package insert:

The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

The Restasis tray label is marked " [redacted] " and " [redacted] " The [redacted] is marked " [redacted] Both tray label and [redacted] indicate the drug product is [redacted]

We have some concerns with the description of this package as a "vial".

Medical Officer's Comments:

Per the CDER Data Standards manual, the proposed single-use LDPE container is a vial.

The [redacted]) is absent from the vial label (see 21 CFR 201.51).

Medical Officer's Comments:

The container is a single-use vial, meant to deliver a single to drop to each eye.

On the tray label, revise [redacted] statement to read: "[redacted]

Medical Officer's Comments:

In the clinical trials performed by the applicant in support of the efficacy and safety of the drug product, dosing took place approximately 12 hours apart.

This reviewer does not agree that the suggested revision to the [redacted] is appropriate.

We suggest substitution of the word "[redacted]" for the Greek "μL", as μ[L] is frequently mistaken for m[L], particularly with scripted instructions.

Medical Officer's Comments:

This reviewer does not agree that the suggested substitution of the word "[redacted]" for the Greek "μL" is appropriate. There could be no substitution of Restasis with a [redacted] concentration since none exits.

Topical ophthalmic prostaglandins are expressed in microliter concentrations with "μL."

Under How Supplied, delete the phrase "fill in 0.9 mL LDPE vial", as inclusion of the empty container size frequently creates confusion over the actual contents and has resulted in medication errors on numerous occasions.

Medical Officer's Comments:

The How Supplied *section of the labeling accurately describes the packaging of the product:*

RESTASIS™ is packaged in single use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 32 vials are packaged in a polypropylene tray with an aluminum peelable lid.

All topical prescription ophthalmic products are similarly described. Since the LDPE vial is a sealed container for single-use, it is unclear how confusion over its contents could result in a medication error.

Recommendations:

It is recommended that NDA 21-023 be approved with the labeling revisions listed in this Medical Officer's Review#5 dated December 1, 2002.

The application supports the safety and effectiveness of Restasis (cyclosporine ophthalmic emulsion) 0.05%

There are no recommendations for additional postmarketing studies.

William M. Boyd, M.D.
Medical Officer

NDA 21-023
HFD-550/Div Files
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/s/

William Boyd
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Wiley Chambers
12/16/02 02:42:39 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-023
Amendment and
Safety Update

NDA 21-023	**Submissions:**	September 7, 2001 April 23, 2002 June 17, 2002 July 11, 2002 September 6, 2002 November 15, 2002
Medical Officer's Review #5	**Review Completed:**	December 13, 2002

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: immunomodulator

Proposed Indication: [redacted]

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

Submitted:

Responses dated September 7, 2001, April 23, 2002, June 17, 2002, July 11, 2002, September 6, 2002, and November 15, 2002, to items identified in the approvable letter dated March 25, 2000, for NDA 21-023 Restasis (cyclosporine ophthalmic emulsion) 0.05%.

Submitted in the November 15, 2002 submission is a revised draft labeling, revised annotated labeling, and safety updates for Studies 192371-005, 192371-501, and 192371-503.

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Overview of the Sponsor's Clinical Response:

This response presents study data from an analysis of the two Phase 3 studies 192371-002 and 192371-002 in support of NDA approval. The analysis is for patients who achieved an increase in Schirmer wetting scores of ≥ 10 mm at the six-month timepoint.

Also submitted, at the agency's request, is a responder analysis of Allergan study 192371-501 (Europe) and Allergan study 192371-503 (Europe).

Validation of the clinical relevance of this clinical sign (increase in Schirmer wetting scores of ≥ 10 mm at the six-month timepoint) is provided.

Validation of the Clinical Relevance of the Clinical Sign:

The sponsor has reviewed available databases to validate clinical relevance of proposed clinical sign (increase in Schirmer wetting scores ≥ 10 mm at the six-month timepoint). Per the sponsor, subjects with lower Schirmer scores have more disability due to dry eye and more ocular surface staining.

These databases included the Henry Ford Heath System validation study of the OSDI (Ocular Surface Disease Index), Allergan study 192371-501 (Europe), and Allergan study 192371-503 (Europe).

Table 1: Validation – Schirmer Score as Clinically Relevant Endpoint

	HFHS (OSDI)[1]				192371-503[2]			
	Group 1 ≤ 5mm N = 36	Group 2 6-10 N = 43	Group 3 ≥11 N = 58	p-value	Group 1 ≤ 5mm N = 110	Group 2 6-10 N = 69	Group 3 ≥11 N = 47	p-value
OSDI symptom subscale	0.31	0.27	0.16	0.004	0.38	0.31	0.30	0.025
OSDI overall score	0.24	0.24	0.14	0.013	0.44	0.37	0.35	0.044
Corneal Staining	1.67	1.12	0.72	0.028	1.9	1.2	0.9	< 0.001

[1] analyses performed on data obtained at single visit

[2] analyses performed on data obtained at week 24

Reviewer's Comments:

Both the OSDI symptom subscale and the OSDI overall score are statistically significantly lower in subjects with Schirmer wetting scores of ≥ 11 mm. There are also statistically significantly lower corneal staining scores in subjects with Schirmer wetting scores of ≥ 11 mm.

Table 2: Correlation coefficients with confidence intervals for validation analyses on HFHS and 192371-503

	HFHS (OSDI)			192371-503		
	Group 1 ≤ 5mm N = 20	Group 2 6-10 N = 28	Group 3 ≥11 N = 89	Group 1 ≤ 5mm N = 110	Group 2 6-10 N = 69	Group 3 ≥11 N = 47
OSDI symptom subscale	-0.131 (-0.54, 0.33)	-0.237 (-0.56, 0.15)	-0.045 (-0.25, 0.16)	0.034 (-0.15, 0.22)	-0.088 (-0.32, 0.15)	0.032 (-0.26, -0.03)
OSDI overall score	-0.303 (-0.66, 0.16)	-0.060 (-0.42, 0.32)	0.001 (-0.21, 0.21)	0.063 (-0.13, 0.25)	-0.104 (-0.33, 0.14)	0.008 (-0.27, -0.02)
Corneal Staining	-0.332 (-0.68, 0.13)	-0.003 (-0.38, 0.37)	-0.080 (-0.28, 0.13)	-0.1158 (-0.30, 0.07)	-0.007 (-0.24, 0.23)	-0.166 (-0.43, 0.13)

Reviewer's Comments:

None of the submitted correlation coefficients approach 1 (or –1), and based on the confidence intervals provided, very few of the coefficients reach statistical significance.

Table 3 summarizes additional analyses from the sponsor showing the percentage of subjects with a corneal staining score of 0, grouped by absolute values of Schirmer, in the ITT population excluding ocular anti-inflammatory drugs and punctal plugs for 192371-002, -003, -501, -503.

If an increase in Schirmer score above 11 mm were clinically relevant, these groups should show less ocular surface staining in 192371-002, -003, -501, -503.

[Note: responders here are patients who achieved an increase in Schirmer wetting scores ≥ 10 mm at the six-month timepoint.]

Table 3: Corneal Staining at Month 6
Percent of Patients with a Corneal Staining Score of Zero

Corneal Staining	192371-002				192371-003			
	Group 1 ≤ 5mm	Group 2 6-10	Group 3 ≥11	p-value	Group 1 ≤ 5mm	Group 2 6-10	Group 3 ≥11	p-value
N	146	89	77	0.005	234	93	57	<0.001
Mean	2.2	1.8	1.6		2.1	1.4	1.1	
Responder[1]	12 (8%)	11 (12%)	11 (14%)	0.301	34 (15%)	22 (24%)	16 (28%)	0.022

[1]responder analysis is the number (percent) of patients with a corneal staining score of 0 at month 6

Corneal Staining	192371-501				192371-503			
	Group 1 ≤ 5mm	Group 2 6-10	Group 3 ≥11	p-value	Group 1 ≤ 5mm	Group 2 6-10	Group 3 ≥11	p-value
N	244	69	32	<0.001	103	53	29	<0.001
Mean	2.3	1.7	1.6		2.0	1.2	0.7	
Responder[1]	16 (7%)	11 (16%)	12 (38%)	<0.001	16 (16%)	17 (32%)	12 (41%)	0.005

[1]responder analysis is the number (percent) of patients with a corneal staining score of 0 at month 6

Reviewer's Comments:

Three of the clinical trials demonstrated statistical significance in the number (percentage) of patients with a corneal staining score of 0 at month 6 when subjects are grouped by absolute values of Schirmer. The remaining trial demonstrates a trend favoring less corneal staining when Schirmer's is ≥11 mm at month 6.

[Note: responders here are patients who achieved a corneal staining score of 0 at month 6.]

Responder Analysis:

Table 4: Responder Analysis - Month 6 – 192371-002, -003

	192371-002				192371-003			
	0.05% cyclo	0.1% cyclo	vehicle	p-value	0.05% cyclo	0.1% cyclo	vehicle	p-value
ITT	20/117 (17%)	11/113 (10%)	11/109 (10%)	0.14735	16/137 (12%)	11/131 (8%)	2/134 (1%)	0.00659
ITT – Anti-Inflammatory Rx and Plugs	10/109 (18%)	10/106 (9%)	8/97 (8%)	0.04825	15/129 (12%)	11/125 (9%)	2/130 (2%)	0.00767
Sjögrens	8/37 (22%)	2/36 (6%)	2/35 (6%)	0.01920	5/57 (9%)	2/46 (4%)	0/54 (0%)	0.06704
Sjögrens - Anti-Inflammatory Rx and Plugs	8/34 (24%)	1/32 (3%)	1/31 (3%)	0.00823	5/53 (9%)	2/43 (5%)	0/52 (0%)	0.04907

Reviewer's Comments:

Specific dry eye populations are identified and analyzed for patients who achieved an increase in Schirmer wetting scores ≥ 10 mm at the six-month timepoint (responders). In Table 1, all of the populations trend towards higher responder rates for the 0.05% cyclosporine treatment group.

In two of the groups (ITT – anti-inflammatory Rx and punctal plugs and Sjögrens - anti-inflammatory Rx and punctal plugs), the responder rates are statistically significant favoring 0.05% cyclosporine in both trials.

Table 5: Responder Analysis - Month 6 – 192371-501, -503

	192371-501				192371-503		
	0.05% cyclo	0.1% cyclo	vehicle	p-value	0.05% cyclo	Refresh	p-value
ITT – Anti-Inflammatory Rx and Plugs	7/109 (6%)	9/120 (8%)	4/116 (3%)	0.41295	11/93 (12%)	7/93 (8%)	0.53511

Reviewer's Comments:

The responder analyses of 192371-501 and 192371-503 (Table 2) do not achieve statistical significance for the specific dry eye population ITT – anti-inflammatory Rx and punctal plugs. The sample sizes are small.

There is a trend towards higher responder rates for the 0.05% cyclosporine treatment groups.

Although –501 and –503 analyses did not achieve statistical significance, the responder analyses are supportive of the findings in –002 and –003.

Safety Update

Information contained in this safety update is comparable to previous safety information reviewed for the original NDA.

The most common adverse event following the use of this drug product is ocular burning (17%). Other events reported in 1% to 5% of patients include conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Original conclusions regarding the safety of 0.05% cyclosporine ophthalmic emulsion in the [redacted] are not altered.

APPEARS THIS WAY
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6 Draft Labeling Page(s) Withheld

Conclusions:

1) A clinically relevant, dry eye population (ITT – ocular anti-inflammatory Rx and punctal plugs) demonstrated statistically significant differences in responder rates for the number of patients who achieved an increase in Schirmer wetting scores ≥ 10 mm at the six-month timepoint in 192371-002 and –003.

   Although –501 and –503 analyses did not achieve statistical significance, the responder analyses are supportive of the findings in –002 and –003.

2) Regarding validation of this clinical sign:

   Both the OSDI symptom subscale and the OSDI overall score are statistically significantly lower in subjects with Schirmer wetting scores of ≥ 11 mm in the validation studies. There are also statistically significantly lower corneal staining scores in subjects with Schirmer wetting scores of > 11 mm in the validation studies.

3) Allergan has successfully demonstrated that the clinical sign (increase in Schirmer wetting scores ≥ 10 mm at the six-month timepoint) is clinically relevant. Lower Schirmer scores seem to have more disability due to dry eye and more ocular surface staining.

4) Original conclusions regarding the safety of 0.05% cyclosporine ophthalmic emulsion in [redacted] are not altered.

Recommendations:

It is recommended that NDA 21-496 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Restasis (cyclosporine ophthalmic emulsion) 0.05%

There are no recommendations for additional postmarketing studies.

William M. Boyd, M.D.
Medical Officer

NDA 21-023
HFD-550/Div Files
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William Boyd
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Wiley Chambers
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Medical Officer's Review of NDA 21-023
Amendment

NDA 21-023	Submission: 10/3/00
Medical Officer's Review #4	Review Completed: 10/5/00

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: Immunomodulator

Proposed Indication: [redacted]

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

Submitted:

Response dated October 3, 2000, to items identified in the approvable letter dated March 25, 2000, for NDA 21-023 Restasis (cyclosporine ophthalmic emulsion) 0.05%.

Sponsor's Clinical Response Overview:

This response presents study data from a keratoconjunctivitis sicca subpopulation at high risk for more severe disease to demonstrate that studies 192371–002 and –003 are replicative and that 0.05% cyclosporine ophthalmic emulsion is effective.

To demonstrate replication in the two Phase 3 studies and to demonstrate the efficacy of 0.05% cyclosporine emulsion, Allergan has performed new analyses beyond the 6-month ITT analyses originally submitted in NDA 21-023.

A clinically relevant keratoconjunctivitis sicca subpopulation consisting of two subgroups has been defined:

1) Sjögren's patients and patients with other autoimmune connective tissue diseases
2) Women 65 years of age or older

This subpopulation excludes patients with major protocol violations including the use of topical ocular corticosteroids.

Reviewer's Comments:

Significant protocol violations included:

1) *prohibited diseases (severe acne rosacea, severe migraine, Grave's disease)*
2) *prohibited surgeries during study*
3) *use of prohibited medications for surgeries*
4) *use of prohibited ocular ointments, pilocarpine, ocular NSAID, beta-blocker, or ocular steroids.*

Analyses were limited to presenting the proportions of patients with zero severity score for one sign (temporal corneal staining) and one symptom (blurred vision) at Month 6.

Description of Patients in the High-Risk Patient Subpopulation:

There are no statistically significant differences in the subpopulation demographic variables between treatment groups for age, age-by-group, sex, race, or iris color in studies 192371–002 and –003.

Table 1 - Numbers of Patients in the High-Risk Patient Subpopulation

Treatment Group	Study 192371-002		Study 192371-003	
	Subpopulation	Original Intent-to-Treat Population	Subpopulation	Original Intent-to-Treat Population
0.05% Cyclosporine	57	135	73	158
0.1% Cyclosporine	52	134	76	158
Vehicle	48	136	68	156

Across both studies, 374 (43%) of the original 877 ITT patients were retained in the high-risk subpopulation of patients. This subpopulation contains less than half of the patients enrolled in each study.

Table 2 – Disease History of the High Risk Patient Subpopulation
(subjects could appear in more than one disease category)

	Study 192371-002			Study 192371-003		
	0.05% CsA	0.1% CsA	Vehicle	0.05% CsA	0.1% CsA	Vehicle
	n=57	n=52	n=48	n=73	n=76	n=68
Post-menopausal	37 (65%)	30 (58%)	30 (63%)	40 (55%)	44 (58%)	35 (52%)
Sjögren's Syndrome	31 (54%)	33 (64%)	27 (56%)	46 (63%)	40 (52%)	48 (71%)
Rheumatoid Arthritis	8 (14%)	10 (19%)	8 (17%)	11 (15%)	12 (16%)	9 (13%)
Scleroderma	2 (4%)	1 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (2%)
Systemic Lupus Erythematosis	1 (2%)	6 (11.5%)	6 (13%)	7 (10%)	8 (11%)	2 (3%)
Sarcoidosis	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Felty's Syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Connective tissue disease	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Crest's syndrome	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Inflammatory Bowel Disease	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 3 - Numbers of Patients in the High-Risk Patient Subpopulation by Sex

Treatment Group	Study 192371-002		Study 192371-003	
	Men	Women	Men	Women
0.05% Cyclosporine	5 (9%)	52 (91%)	5 (7%)	68 (93%)
0.1% Cyclosporine	3 6%)	49 (94%)	1 (1%)	75 (99%)
Vehicle	3 (6%)	45 (94%)	6 (9%)	56 (91%)

Reviewer's Comments:

Although selected post-hoc, the selection of this subpopulation of patients and the resultant analysis are not fundamentally flawed. The selection criteria used to describe the subpopulation are sound, reasonable, and relevant clinically.

There are, however, a very small number of male patients remaining in each Study versus the original keratoconjunctivitis population.

Statistical Methods:

A subgroup analysis was performed for patients with keratoconjunctivitis sicca in the high-risk subpopulation. As described in the original submission for NDA 21-023, for efficacy variables collected on both eyes, a "worse" eye was selected.

As month 6 has been identified as the primary time point, only the month-6 results are presented here. Within the high-risk subpopulation, those patients have been evaluated where the sign or symptom was zero at the month 6 time point.

Reviewer's Comments:

The alpha value of 0.05 *must be lowered to account for the number of comparisons being performed. The Bonferroni correction (a conservative multiple-comparison correction used when several independent statistical tests are performed simultaneously) sets the alpha value for the entire set of* n *comparisons equal to* α *by taking the alpha value for each comparison equal to* α / n.

In this case: α / n = 0.05/2 = 0.025. *Both an objective sign and a subjective symptom of dry eye must demonstrate significance at* $\alpha = 0.025$.

Staining

Results are shown below for Temporal Conjunctival Staining. There is a statistically significant difference in the percent of patients without this sign at the month 6 timepoint.

Table 4 – Temporal Conjunctival Staining* (Percentage of Sign Equaling Zero)

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=57	CsA 0.1% n=52	Vehicle n=48	CsA 0.05% n=73	CsA 0.1% n=76	Vehicle n=68
Month 6	17/57 (30%)	9/52 (17%)	5/48 (10%)	18/73 (25%)	18/76 (24%)	7/68 (10%)
P-value for pairwise comparisons vs. vehicle	0.02539	0.47703	NA	0.00714	0.03664	NA

*on a six-point severity scale (grades 0 to 5) using worse eye

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this objective sign.

Blurred Vision

Results are shown below for Blurred Vision. There is a statistically significant difference in the percent of patients without this symptom at the month 6 timepoint.

Table 5 – Blurred Vision* (Percentage of Symptom Equaling Zero)

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=56	CsA 0.1% n=52	Vehicle n=48	CsA 0.05% n=73	CsA 0.1% n=75	Vehicle n=67
Month 6	20/56 (36%)	11/52 (21%)	9/48 (19%)	25/73 (30%)	22/75 (29%)	11/67 (16%)
P-value for pairwise comparisons vs. vehicle	0.02222	0.86091	NA	0.01971	0.05105	NA

*measured on a 0 (no symptom) to 4 (always notice symptom) scale

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this subjective symptom.

Conclusions:

On October 10, 2000, NDA 21-023 was referred to the CDER Pre-Decisional Committee for discussion of 0.05% cyclosporine ophthalmic emulsion's use

The committee gave the opinion that efficacy could not be adequately demonstrated when the overall study population results did not show statistical significance.

The committee recommended that the sponsor perform an additional clinical trial to adequately demonstrate efficacy

Recommendations:

The sponsor should submit additional information to support the efficacy of 0.05% cyclosporine ophthalmic emulsion

Specifically, the sponsor should perform an additional clinical trial to adequately demonstrate efficacy

/S/

William M. Boyd, M.D.
Medical Officer

cc: NDA 21-023
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers /S/
HFD-550/Acting Div Director/Bull
HFD-725/Stat/LuHo
HFD-805/Micro/Riley
HFD-550/Chem/Tso
HFD-550/PM/Gorski
HFD-340/Carreras
HFD-550/PharmTox/Mukherjee

Medical Officer's Review of NDA 21-023
Amendment

NDA 21-023
Medical Officer's Review #3

Submission: 10/2/00
Review Completed: 10/3/00

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: Immunomodulator

Proposed Indication: [redacted]

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

Submitted:

Response dated October 2, 2000, to items identified in the approvable letter dated March 25, 2000, for NDA 21-023 Restasis (cyclosporine ophthalmic emulsion) 0.05%.

Sponsor's Clinical Response Overview:

This response presents study data from a keratoconjunctivitis sicca subpopulation at high risk for more severe disease to demonstrate that studies 192371–002 and –003 are replicative and that 0.05% cyclosporine ophthalmic emulsion is effective.

To demonstrate replication in the two Phase 3 studies and to demonstrate the efficacy of 0.05% cyclosporine emulsion, Allergan has performed new analyses beyond the 6-month ITT analyses originally submitted in NDA 21-023.

A clinically relevant keratoconjunctivitis sicca subpopulation consisting of two subgroups has been defined:

1) Sjögren's patients and patients with other autoimmune connective tissue diseases
2) Women 65 years of age or older (receiving no hormone replacement therapy or estrogen hormone replacement therapy alone).

Analyses were limited to presenting the proportions of patients with zero severity score for one sign (temporal corneal staining) and one symptom (blurred vision) at Month 6.

Reviewer's Comments:

In a telephone conversation held on September 28, 2000, between the Sponsor and Dr. Wiley Chambers, the second component of the clinically relevant keratoconjunctivitis sicca subpopulation was specified to consist of all women 65 years of age or older.

The Sponsor has excluded patients taking hormone replacement therapy with the exception of estrogen replacement therapy alone.

The keratoconjunctivitis sicca subpopulation presented in this submission is not clinically justifiable.

Description of Patients in the High-Risk Patient Subpopulation:

There are no statistically significant differences in the subpopulation demographic variables between treatment groups for age, age-by-group, sex, race, or iris color in studies 192371–002 and –003.

Table 1 - Numbers of Patients in the High-Risk Patient Subpopulation

Treatment Group	Study 192371-002		Study 192371-003	
	Subpopulation	Original Intent-to-Treat Population	Subpopulation	Original Intent-to-Treat Population
0.05% Cyclosporine	45	135	64	158
0.1% Cyclosporine	42	134	61	158
Vehicle	42	136	62	156

Across both studies, 316 (36%) of the original 877 ITT patients were retained in the high-risk subpopulation of patients. This subpopulation contains less than half of the patients enrolled in each study.

Table 2 – Disease History of the High Risk Patient Subpopulation
(subjects could appear in more than one disease category)

	Study 192371-002			Study 192371-003		
	0.05% CsA	0.1% CsA	Vehicle	0.05% CsA	0.1% CsA	Vehicle
	n=45	n=42	n=42	n=64	n=61	n=62
Post-menopausal	27 (60%)	23 (55%)	25 (60%)	31 (48%)	34 (56%)	29 (47%)
Sjögren's Syndrome	23 (51%)	25 (60%)	22 (52%)	41 (64%)	27 (44%)	41 (66%)
Rheumatoid Arthritis	6 (13%)	5 (12%)	7 (17%)	8 (13%)	9 (15%)	10 (16%)
Scleroderma	2 (4%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Systemic Lupus Erythematosis	2 (4%)	4 (10%)	4 (10%)	7 (11%)	5 (8%)	0 (0%)
Sarcoidosis	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Felty's Syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Connective tissue disease	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Crest's syndrome	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Inflammatory Bowel Disease	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 3 - Numbers of Patients in the High-Risk Patient Subpopulation by Sex

Treatment Group	Study 192371-002		Study 192371-003	
	Men	Women	Men	Women
0.05% Cyclosporine	5 (11%)	40 (89%)	5 (8%)	59 (92%)
0.1% Cyclosporine	4 (10%)	38 (90%)	1 (2%)	60 (98%)
Vehicle	4 (10%)	38 (90%)	6 (10%)	56 (90%)

Reviewer's Comments:

Although selected post-hoc, the selection of a subpopulation of patients and the resultant analysis are acceptable for the evaluation of this condition. The selection criteria used to describe the subpopulation are sound, reasonable, but not clinically justifiable (see Reviewer's Comments, page 2).

There are a very small number of male patients remaining in each Study versus the original keratoconjunctivitis population.

Statistical Methods:

A subgroup analysis was performed for patients with keratoconjunctivitis sicca in the high-risk subpopulation. As described in the original submission for NDA 21-023, for efficacy variables collected on both eyes, a "worse" eye was selected.

As month 6 has been identified as the primary time point, only the month-6 results are presented here. Within the high-risk subpopulation, those patients have been evaluated where the sign or symptom was zero at the month 6 time point.

Staining

Results are shown below for Temporal Conjunctival Staining. There is a statistically significant difference in the percent of patients without this sign at the month 6 timepoint.

Table 4 – Temporal Conjunctival Staining* (Percentage of Sign Equaling Zero)

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=45	CsA 0.1% n=42	Vehicle n=42	CsA 0.05% n=64	CsA 0.1% n=60	Vehicle n=62
Month 6	14/45 (31%)	8/42 (19%)	3/42 (7%)	15/64 (23%)	18/60 (30%)	6/62 (10%)
Among-group p-value	0.05107			0.02009		
P-value for pairwise comparisons vs. vehicle	0.01530	0.20786	NA	0.04909	0.00569	NA

*on a six-point severity scale (grades 0 to 5) using worse eye

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this objective sign.

Blurred Vision

Results are shown below for Blurred Vision. There is a statistically significant difference in the percent of patients without this symptom at the month 6 timepoint.

Table 5 – Blurred Vision* (Percentage of Symptom Equaling Zero)

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=44	CsA 0.1% n=42	Vehicle n=42	CsA 0.05% n=64	CsA 0.1% n=60	Vehicle n=61
Month 6	18/44 (41%)	9/42 (21%)	8/42 (19%)	19/64 (30%)	19/60 (32%)	8/61 (13%)
Among-group p-value	0.01182			0.02843		
P-value for pairwise comparisons vs. vehicle	0.00603	0.65844	NA	0.03077	0.01100	NA

*measured on a 0 (no symptom) to 4 (always notice symptom) scale

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this subjective symptom.

Conclusions:

The analyses submitted on October 2, 2000, are not sufficient to establish the efficacy of Restasis

The keratoconjunctivitis sicca subpopulation presented in this submission is not clinically justifiable. The Sponsor has excluded patients taking hormone replacement therapy with the exception of estrogen replacement therapy alone. This is not acceptable.

Recommendations:

The sponsor should submit additional information to support the efficacy of 0.05% cyclosporine ophthalmic emulsion

/S/

William M. Boyd, M.D.
Medical Officer

cc: NDA 21-023
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers /S/
HFD-550/Acting Div Director/Bull
HFD-725/Stat/LuHo
HFD-805/Micro/Riley
HFD-550/Chem/Tso
HFD-550/PM/Gorski
HFD-340/Carreras
HFD-550/PharmTox/Mukherjee

Medical Officer's Review of NDA 21-023
Amendment

NDA 21-023		Submissions:	8/9/00, 9/7/00
Medical Officer's Review #2		Review Completed:	9/21/00

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: Immunomodulator

Proposed Indication: [redacted]

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

Submitted:

I. Response dated August 9, 2000, to items identified in the approvable letter dated March 25, 2000, for NDA 21-023 Restasis (cyclosporine ophthalmic emulsion) 0.05%.

II. Clinical Amendment dated September 7, 2000.

I. Sponsor's Clinical Response Overview:

This response presents study data from a keratoconjunctivitis sicca subpopulation at high risk for more severe disease to demonstrate that studies 192371–002 and –003 are replicative and that 0.05% cyclosporine ophthalmic emulsion is effective.

To demonstrate replication in the two Phase 3 studies and to demonstrate the efficacy of 0.05% cyclosporine emulsion, Allergan has performed new analyses beyond the 6-month ITT analyses originally submitted in NDA 21-023.

A clinically relevant keratoconjunctivitis sicca subpopulation consisting of two subgroups has been defined:

1) Sjögren's patients and patients with other autoimmune connective tissue diseases
2) Post-menopausal woman (receiving no hormone replacement therapy or estrogen hormone replacement therapy alone).

Analyses were limited to presenting the proportions of patients with zero severity score for one sign (temporal conjunctival staining) and one symptom (blurred vision) at Month 6.

Description of Patients in the High-Risk Patient Subpopulation:

There are no statistically significant differences in the subpopulation demographic variables between treatment groups for age, age-by-group, sex, race, or iris color in studies 192371-002 and -003.

Table 1 - Numbers of Patients in the High-Risk Patient Subpopulation

Treatment Group	Study 192371-002		Study 192371-003	
	Subpopulation	Original Intent-to-Treat Population	Subpopulation	Original Intent-to-Treat Population
0.05% Cyclosporine	52	135	67	158
0.1% Cyclosporine	43	134	59	158
Vehicle	46	136	67	156

Across both studies, 334 (38%) of the original 877 ITT patients were retained in the high-risk subpopulation of patients. This subpopulation contains less than half of the patients enrolled in each study.

Table 2 – Disease History of the High Risk Patient Subpopulation
(subjects could appear in more than one disease category)

	Study 192371-002			Study 192371-003		
	0.05% CsA	0.1% CsA	Vehicle	0.05% CsA	0.1% CsA	Vehicle
	n=52	n=43	n=46	n=67	n=59	n=67
Post-menopausal	37 (71%)	26 (61%)	34 (74%)	40 (60%)	45 (76%)	40 (60%)
Sjögren's Syndrome	24 (46%)	25 (58%)	23 (50%)	41 (61%)	28 (48%)	41 (61%)
Rheumatoid Arthritis	6 (12%)	5 (12%)	7 (15%)	8 (12%)	9 (15%)	10 (15%)
Scleroderma	2 (4%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Systemic Lupus Erythematosis	2 (4%)	4 (9%)	4 (9%)	7 (10%)	5 (9%)	0 (0%)
Sarcoidosis	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Felty's Syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Connective tissue disease	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Crest's syndrome	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Inflammatory Bowel Disease	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 3 - Numbers of Patients in the High-Risk Patient Subpopulation by Sex

Treatment Group	Study 192371-002		Study 192371-003	
	Men	Women	Men	Women
0.05% Cyclosporine	5 (10%)	47 (90%)	5 (8%)	62 (92%)
0.1% Cyclosporine	4 (9%)	39 (91%)	1 (2%)	58 (98%)
Vehicle	4 (9%)	42 (91%)	6 (9%)	61 (91%)

Reviewer's Comments:

Although selected post-hoc, the selection of this subpopulation of patients and the resultant analysis are not fundamentally flawed. The selection criteria used to describe the subpopulation are sound, reasonable, and relevant clinically.

There are, however, a very small number of male patients remaining in each Study versus the original keratoconjunctivitis population.

Statistical Methods:

A subgroup analysis was performed for patients with keratoconjunctivitis sicca in the high-risk subpopulation. As described in the original submission for NDA 21-023, for efficacy variables collected on both eyes, a "worse" eye was selected.

As month 6 has been identified as the primary time point, only the month-6 results are presented here. Within the high-risk subpopulation (Sjögren's patients, patients with other autoimmune connective tissue diseases, and postmenopausal women receiving estrogen hormone replacement therapy alone), those patients have been evaluated where the sign or symptom was zero at the month 6 time point.

Staining

Results are shown below for Temporal Conjunctival Staining. There is a statistically significant difference in the percent of patients without this sign at the month 6 timepoint.

Table 4 – Temporal Conjunctival Staining* (Percentage of Sign Equaling Zero)

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=52	CsA 0.1% n=43	Vehicle n=46	CsA 0.05% n=66	CsA 0.1% n=58	Vehicle n=67
Month 6	16/52 (31%)	10/43 (23%)	4/46 (9%)	19/66 (29%)	16/58 (28%)	10/67 (15%)
Among-group p-value	0.03880			0.03270		
P-value for pairwise comparisons vs. vehicle	0.01029	0.08832	NA	0.01625	0.04227	NA

*on a six-point severity scale (grades 0 to 5) using worse eye

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this objective sign.

Blurred Vision

Results are shown below for Blurred Vision. There is a statistically significant difference in the percent of patients without this symptom at the month 6 timepoint.

Table 5 – Blurred Vision* (Percentage of Symptom Equaling Zero)

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=51	CsA 0.1% n=43	Vehicle n=46	CsA 0.05% n=67	CsA 0.1% n=58	Vehicle n=66
Month 6	19/51 (37%)	10/43 (23%)	7/46 (15%)	20/67 (30%)	21/58 (36%)	10/66 (15%)
Among-group p-value	0.01849			0.02556		
P-value for pairwise comparisons vs. vehicle	0.00635	0.20193	NA	0.04224	0.01049	NA

*measured on a 0 (no symptom) to 4 (always notice symptom) scale

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this subjective symptom.

Review of the submitted datasets revealed that there are numerous women, over the age of 60, who are not listed as postmenopausal and who are not included in the high-risk subgroup (29 subjects in –002, 45 subjects in –003).

Discussion with the Sponsor reveals that women were considered postmenopausal only if their investigator appropriately checked a box on the case report forms. The Agency does not consider this definition of the post-menopausal patient population acceptable.

II. Population A, Population B, and Population C

The Sponsor submitted a Clinical Amendment on September 7, 2000, which redefined the definition of post-menopausal women in the patient population at high risk for keratoconjunctivitis sicca. Included were three separate analyses designated as population a, population b and population c. In each analysis, the population still included Sjögren's patients and patients with other autoimmune connective tissue diseases such as rheumatoid arthritis, scleroderma, and systemic lupus erythematosis:

1) Population A: post-menopausal women whose CRF indicates they are post-menopausal or who are age 65 or greater
2) Population B: post-menopausal women whose CRF indicates they are post-menopausal or who are age 68 or greater
3) Population C: post-menopausal women whose CRF indicates they are post-menopausal or who are age 65 or greater and excluding subjects on topical steroids.

Population A

Table 6 - Numbers of Patients in the High-Risk Patient Subpopulation A

Treatment Group	Study 192371-002		Study 192371-003	
	Subpopulation	Original Intent-to-Treat Population	Subpopulation	Original Intent-to-Treat Population
0.05% Cyclosporine	56	135	73	158
0.1% Cyclosporine	45	134	72	158
Vehicle	52	136	73	156

Table 7 – Temporal Conjunctival Staining* (Percentage of Sign Equaling Zero) in the High-Risk Patient Subpopulation A

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=56	CsA 0.1% n=45	Vehicle n=52	CsA 0.05% n=72	CsA 0.1% n=71	Vehicle n=73
Month 6	18/56 (32%)	10/45 (22%)	4/52 (8%)	20/72 (28%)	23/71 (32%)	11/73 (15%)
Among-group p-value	0.01867			0.03264		
P-value for pairwise comparisons vs. vehicle	0.00451	0.07708	NA	0.03854	0.01247	NA

*on a six-point severity scale (grades 0 to 5) using worse eye

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this objective sign.

Table 8 – Blurred Vision* (Percentage of Symptom Equaling Zero) in the High-Risk Patient Subpopulation A

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=55	CsA 0.1% n=45	Vehicle n=52	CsA 0.05% n=73	CsA 0.1% n=71	Vehicle n=72
Month 6	20/55 (36%)	11/45 (24%)	10/52 (19%)	21/73 (29%)	24/71 (34%)	12/72 (17%)
Among-group p-value	0.04303			0.04984		
P-value for pairwise comparisons vs. vehicle	0.01314	0.06873	NA	0.35443	0.01803	NA

*measured on a 0 (no symptom) to 4 (always notice symptom) scale

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are not statistically significant for Study 192371–003.

Studies 192371–002 and –003 are not replicative for this subjective symptom.

Population B

Table 9 - Numbers of Patients in the High-Risk Patient Subpopulation B

Treatment Group	Study 192371-002		Study 192371-003	
	Subpopulation	Original Intent-to-Treat Population	Subpopulation	Original Intent-to-Treat Population
0.05% Cyclosporine	55	135	71	158
0.1% Cyclosporine	45	134	70	158
Vehicle	51	136	71	156

Table 10 – Temporal Conjunctival Staining* (Percentage of Sign Equaling Zero) in the High-Risk Patient Subpopulation B

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=55	CsA 0.1% n=45	Vehicle n=51	CsA 0.05% n=70	CsA 0.1% n=69	Vehicle n=71
Month 6	17/55 (31%)	10/45 (22%)	4/51 (8%)	20/70 (29%)	22/69 (32%)	11/71 (15%)
Among-group p-value	0.02949			0.03521		
P-value for pairwise comparisons vs. vehicle	0.00750	0.08367	NA	0.02965	0.01780	NA

*on a six-point severity scale (grades 0 to 5) using worse eye

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this objective sign.

Table 11 – Blurred Vision* (Percentage of Symptom Equaling Zero) in the High-Risk Patient Subpopulation B

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=54	CsA 0.1% n=45	Vehicle n=51	CsA 0.05% n=71	CsA 0.1% n=69	Vehicle n=70
Month 6	20/54 (37%)	11/45 (24%)	9/51 (18%)	21/71 (30%)	24/69 (35%)	11/70 (16%)
Among-group p-value	0.02222			0.02410		
P-value for pairwise comparisons vs. vehicle	0.00598	0.24488	NA	0.04234	0.00789	NA

*measured on a 0 (no symptom) to 4 (always notice symptom) scale

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this subjective symptom.

Population C

Table 12 - Numbers of Patients in the High-Risk Patient Subpopulation C

Treatment Group	Study 192371-002		Study 192371-003	
	Subpopulation	Original Intent-to-Treat Population	Subpopulation	Original Intent-to-Treat Population
0.05% Cyclosporine	54	135	72	158
0.1% Cyclosporine	45	134	71	158
Vehicle	51	136	72	156

Table 13 – Temporal Conjunctival Staining* (Percentage of Sign Equaling Zero) in the High-Risk Patient Subpopulation C

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=54	CsA 0.1% n=45	Vehicle n=51	CsA 0.05% n=71	CsA 0.1% n=70	Vehicle n=72
Month 6	18/54 (33%)	10/45 (22%)	4/51 (8%)	19/71 (27%)	22/70 (31%)	10/72 (14%)
Among-group p-value	0.01505			0.02554		
P-value for pairwise comparisons vs. vehicle	0.00365	0.08367	NA	0.03212	0.00863	NA

*on a six-point severity scale (grades 0 to 5) using worse eye

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371–002 and –003 are replicative for this objective sign.

Table 14 – Blurred Vision* (Percentage of Symptom Equaling Zero) in the High-Risk Patient Subpopulation C

	Study 192371-002			Study 192371-003		
	CsA 0.05% n=53	CsA 0.1% n=45	Vehicle n=51	CsA 0.05% n=72	CsA 0.1% n=69	Vehicle n=70
Month 6	20/53 (38%)	11/45 (24%)	10/51 (20%)	21/72 (29%)	24/70 (34%)	11/71 (15%)
Among-group p-value	0.04031			0.02697		
P-value for pairwise comparisons vs. vehicle	0.01261	0.40925	NA	0.04292	0.00959	NA

*measured on a 0 (no symptom) to 4 (always notice symptom) scale

Reviewer's Comments:

In the selected high-risk population, the p-values shown for the pairwise comparisons between cyclosporine ophthalmic emulsion 0.05% and vehicle are statistically significant.

Studies 192371--002 and –003 are replicative for this subjective symptom.

Conclusions:

1) *The analyses submitted on August 9, 2000, are not sufficient to establish the efficacy of Restasis*

The Sponsor's definition of " post-menopausal" is unacceptable. There are numerous women, over the age of 60, who are not listed in the dataset as postmenopausal and who are not included in the high-risk subgroup (29 subjects in –002, 45 subjects in –003).

2) *The analyses submitted on September 7, 2000, are not sufficient to establish the efficacy of Restasis in either Population A, B, or C. The selection criteria used to describe the subpopulations are not sound, reasonable, or relevant clinically.*

The selection of ages 65 and 68 as post-menopausal does not correlate with commonly accepted median ages for the onset of menopause. The North American Menopause Society gives a median age for menopause in the Western world of 51.4 years.

Recommendations:

The sponsor should submit additional information to support the efficacy of 0.05% cyclosporine ophthalmic emulsion:

1) [redacted]

2)

3) [redacted]

4) [redacted]

5) [redacted]

William M. Boyd, M.D.
Medical Officer

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

Medical Officer's Review of NDA 21-023
Original

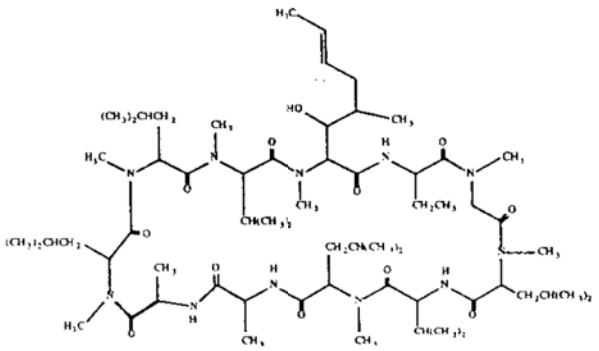
NDA 21-023
Medical Officer's Review

Submission: 2/24/99
Review Completed: 7/27/99

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:

2 Table of Contents **Page**

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 (kg)
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 Kerato-conjunctivitis	Parallel Double-Masked Pharmo-kinetic Levels	cyclo 0.05% cyclo 0.1% common vehicle	135 134 136 total 405	21 – 90 mean 59.3	(21/79) 5/77/18	6 months Treatment Phase 6 months Extension Phase
2	003	Moderate to Severe Kerato-conjunctivitis	Parallel Double-Masked	cyclo 0.05% cyclo 0.1% common vehicle	158 158 156 total 472	24 – 90 mean 59.8	(16/84) 4/91/5	6 months Treatment Phase 6 months Extension Phase
3	001	Moderate to Severe Kerato-conjunctivitis	Parallel Double-Masked Dose-Ranging	cyclo 0.05% cyclo 0.1% cyclo 0.2% cyclo 0.4% vehicle of 0.2%	31 32 34 32 33 total 162	31 – 88 mean 58.6	(16/84) 7/90/3	12 weeks Treatment Phase

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%	Cyclosporine 0.1%	
[redacted]	2697	10	10	10	209-229; 410-418
[redacted]	2702	3	3	3	278-286
[redacted]	0207	11	11	11	194-208; 314-328; 488-490

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

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

[redacted]

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 [redacted] 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 [redacted] during the Vehicle-Controlled Masked Treatment Phase. Additional samples will be drawn at [redacted] For the cyclosporine A AUC evaluations, patients had blood samples collected at [redacted] after the morning dose during [redacted] of the Cyclosporine Treatment Extension Phase.

Study Medications:

- Cyclosporine 0.05% ophthalmic emulsion (Allergan formulation number 9054X), which contained 0.05% cyclosporine [redacted] 0, [redacted]. Supplied in unit dose vials.

- Cyclosporine 0.1% ophthalmic emulsion (Allergan formulation number 8735X), which contained 0.10% [redacted] Supplied in unit dose vials.

- Vehicle of cyclosporine ophthalmic emulsion (Allergan formulation number 8922X), [redacted] 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), [redacted] Supplied in unit dose vials.

Study Masking:

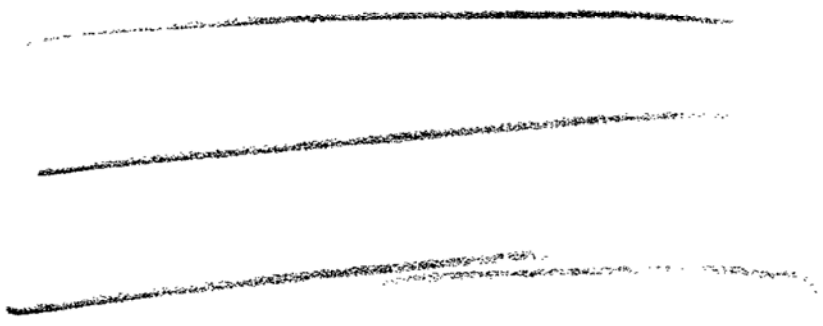
The study medication was packaged, labeled, and masked in a manner consistent with Good Manufacturing Practice (GMP) regulations for investigational supplies. Identical unit-dose vials were used to hold the study treatments, which were each of an identical milky color. The medication was identified as 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 [redacted] equivalent to a Snellen score of [redacted] 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®:

[redacted]

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 aztemizole [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 [redacted] without anesthesia) in [redacted] after nasal stimulation [redacted]
- Patients who responded "N/A" [redacted] times 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

- Corneal disorder or abnormality that affected corneal sensitivity or normal spreading of the tear film (except superficial punctate keratitis)
- Severe blepharitis or obvious inflammation of the lid margin that in the judgment of the investigator may have interfered with the interpretation of the study results
- Occlusion of the lacrimal puncta with temporary punctal plugs within one month prior to the screening visit
- Occlusion of the lacrimal puncta (surgical and permanent) within 3 months prior to the screening visit
- Anticipated use of temporary punctal plugs during the study
- History of anterior segment surgery or trauma that could have affected corneal sensitivity (e.g., cataract surgery or any surgery involving a limbal or corneal incision within the last 12 months)
- KCS secondary to the destruction of conjunctival goblet cells (as with vitamin A deficiency), or scarring (such as that with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation)
- Presence or history of ocular acne rosacea
- Acne rosacea patients who were currently on systemic tetracycline or any other prescribed treatment for acne rosacea
- Patient had a condition or was in a situation that, in the investigator's opinion, may have put the patient at a significant risk, may have confounded the study results, or may have interfered significantly with the patient's participation in the study

Efficacy Criteria:

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

Objective Signs

Corneal Staining

For corneal fluorescein staining, the entire cornea was evaluated using the yellow barrier filter and the slit lamp's cobalt blue illumination. The staining was graded using the Oxford Scheme 6-point scale of severity. A negative change from baseline indicated improvement.

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. The 7-point scale ranged from 0 (completely cleared) to 6 (condition worsened).

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.

Table 4
Schedule of Visits and Measurements

Shading = Measured at selected sites only

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

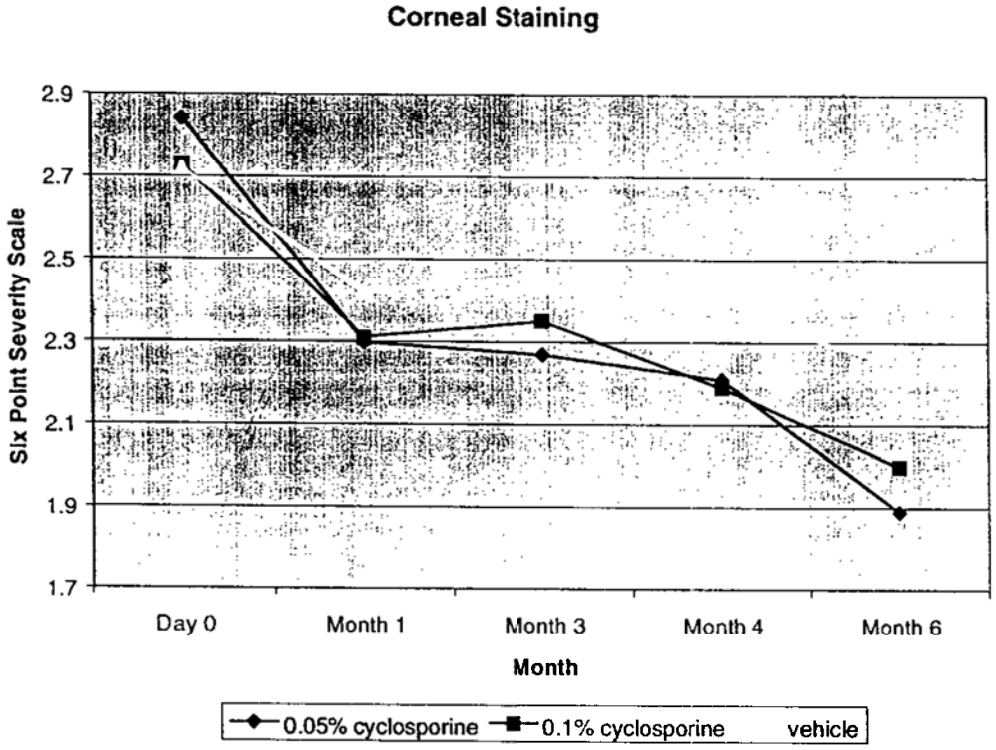
Treatment groups were balanced with respect to age, sex, race, iris color, weight, and height. There were no statistically significant treatment group differences or treatment-by-investigator interactions for these demographic categories.

8.1.1 Efficacy – Objective Signs and Subjective Symptoms

Reviewer's Comments:

Intent-to-treat population unless noted.

Objective Signs

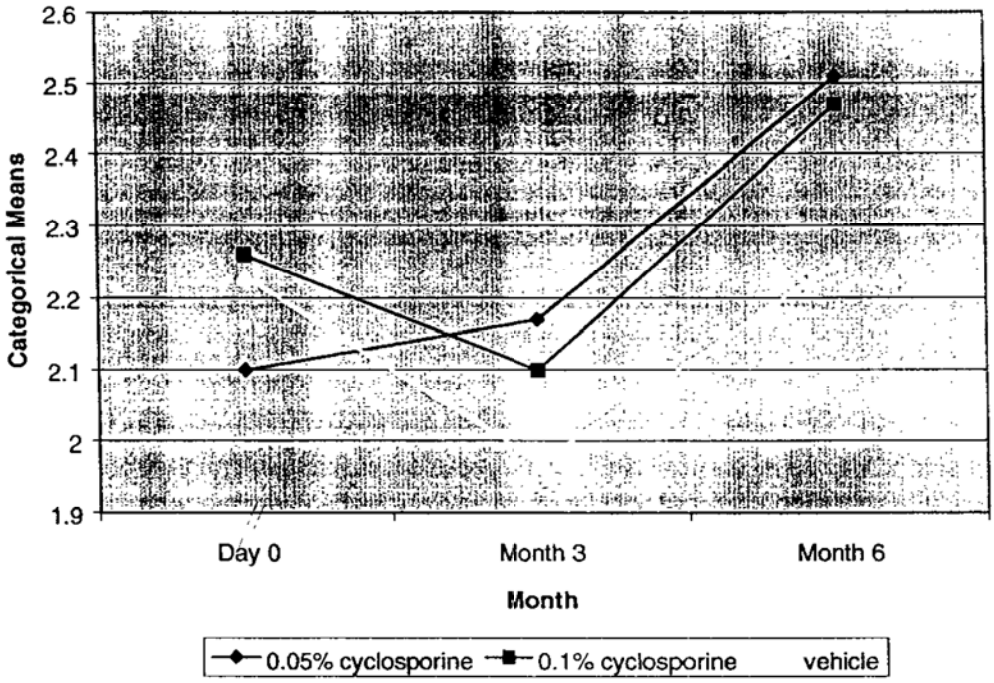


Reviewer's Comments:

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).

Tear Breakup Time

For TBUT 10 seconds, the number of patients is tabulated.
For TBUT < 10 seconds, the three measurements have been averaged for the worse eye.

	TBUT Duration		0.05% cyclosporine (N=135)	0.1% cyclosporine (N=134)	vehicle (N=136)
Day 0	10 seconds	N	N=8	N=9	N=6
	< 10 seconds	N Mean	N=126 3.26	N=124 3.06	N=129 3.09
Month 3	10 seconds	N	N=5	N=7	N=4
	< 10 seconds	N Mean	N=81 3.00	N=77 2.48	N=82 2.95
Month 4	10 seconds	N	N=7	N=10	N=2
	< 10 seconds	N Mean	N=107 2.97	N=101 2.77	N=105 3.08
Month 6	10 seconds	N	N=10	N=4	N=3
	< 10 seconds	N Mean	N=125 3.31	N=124 3.05	N=127 3.29

Reviewer's Comments:

TBUT is similar across groups at baseline. For patients with TBUT < 10 seconds, the average baseline TBUT was approximately 3 seconds and remained so at month 6. Statistical significance was not calculated for this variable.

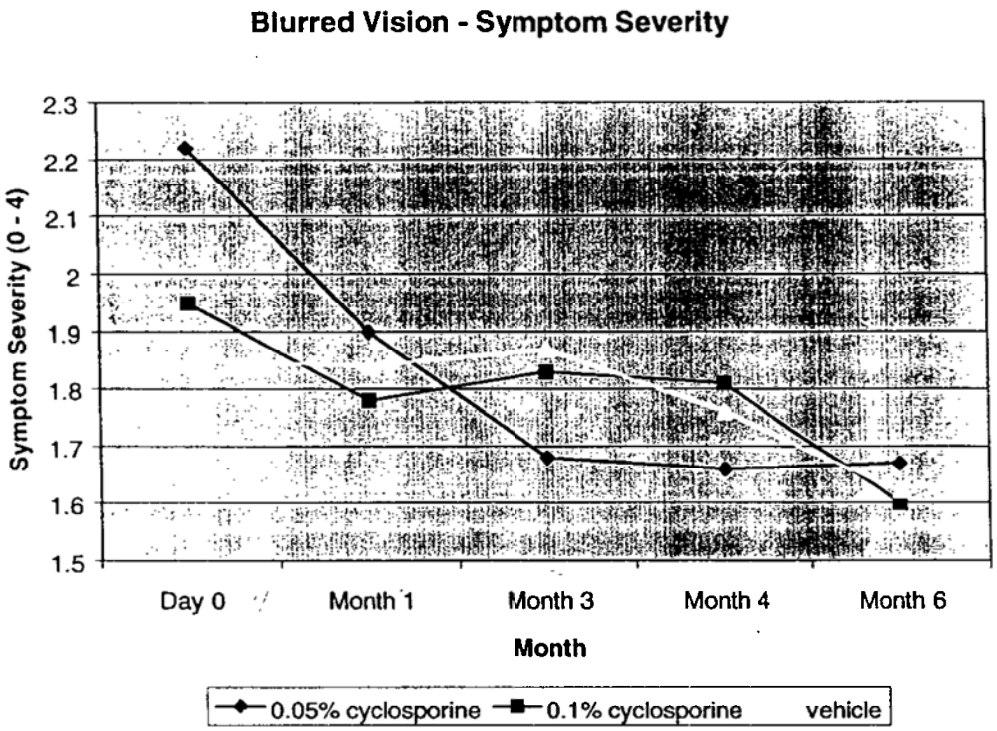
Sum of Corneal and Interpalpebral Conjunctival Staining

Among-group differences were statistically significant at months 4 and 6 (p = 0.050 and 0.044). At these visits, pairwise comparisons were statistically significant for 0.05% cyclosporine versus vehicle.

Other Objective Signs

There are no statistically significant among-group differences found for 1) nasal or temporal interpalpebral conjunctival staining, 2) the sum of nasal and temporal interpalpebral conjunctival staining, or 4) Schirmer values without anesthesia.

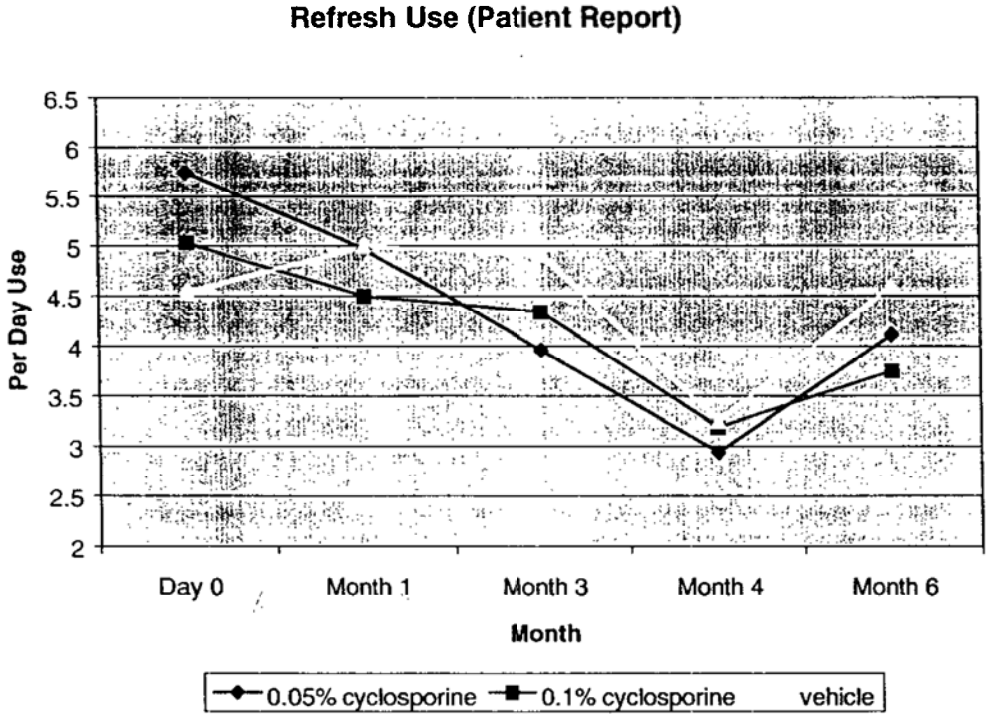
Subjective Symptoms



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).



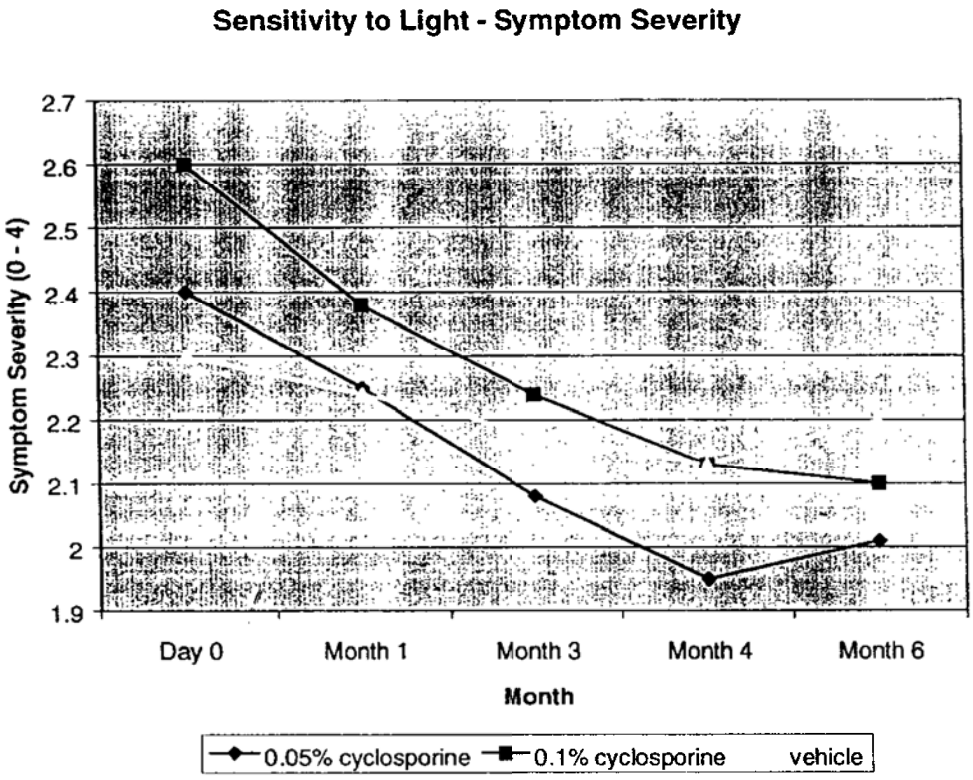
Reviewer's Comments:

Refresh Use

A negative change from baseline indicates improvement.

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

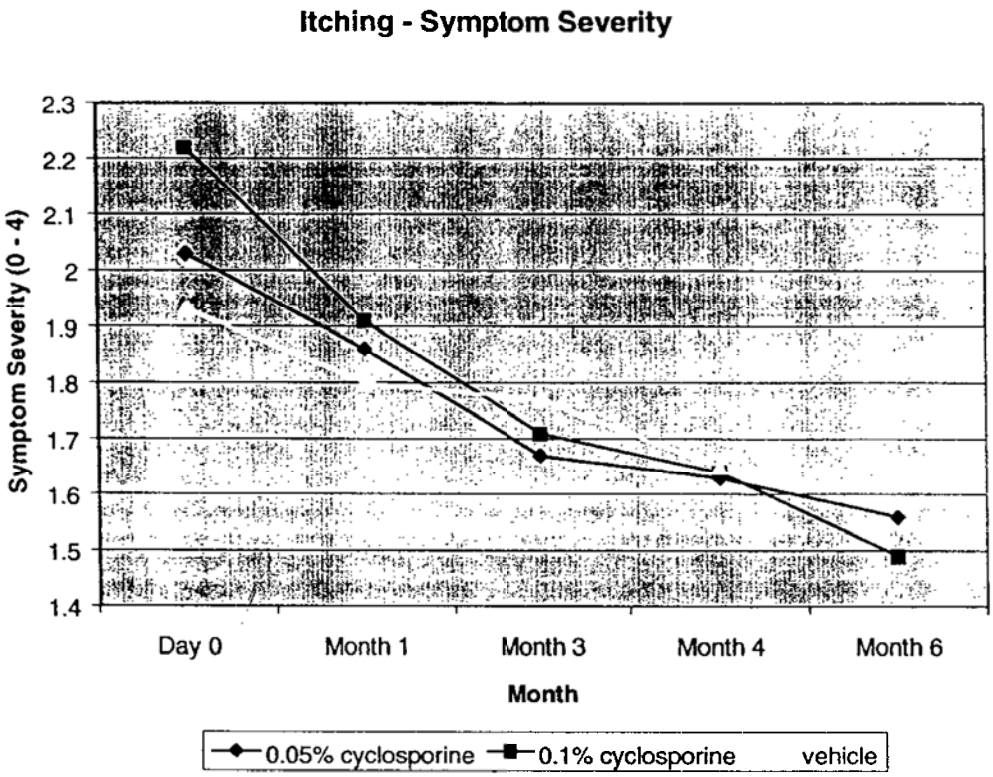
There is a statistically significant among-group difference at month 3, favoring 0.05% cyclosporine over vehicle (p = 0.028).



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 0.05% cyclosporine over vehicle (p = 0.020 and 0.008).

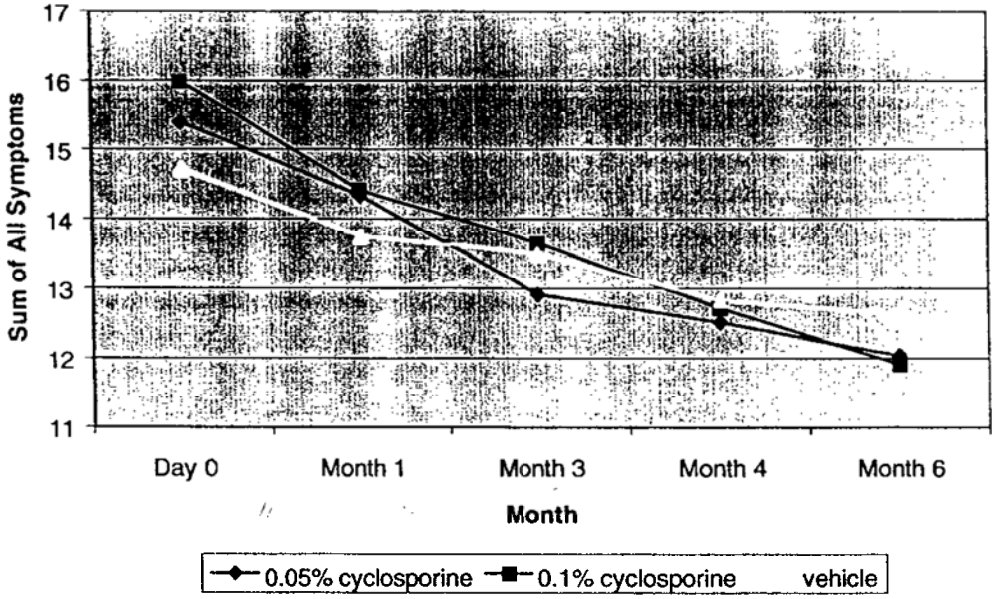


Reviewer's Comments:

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, and 0.004).

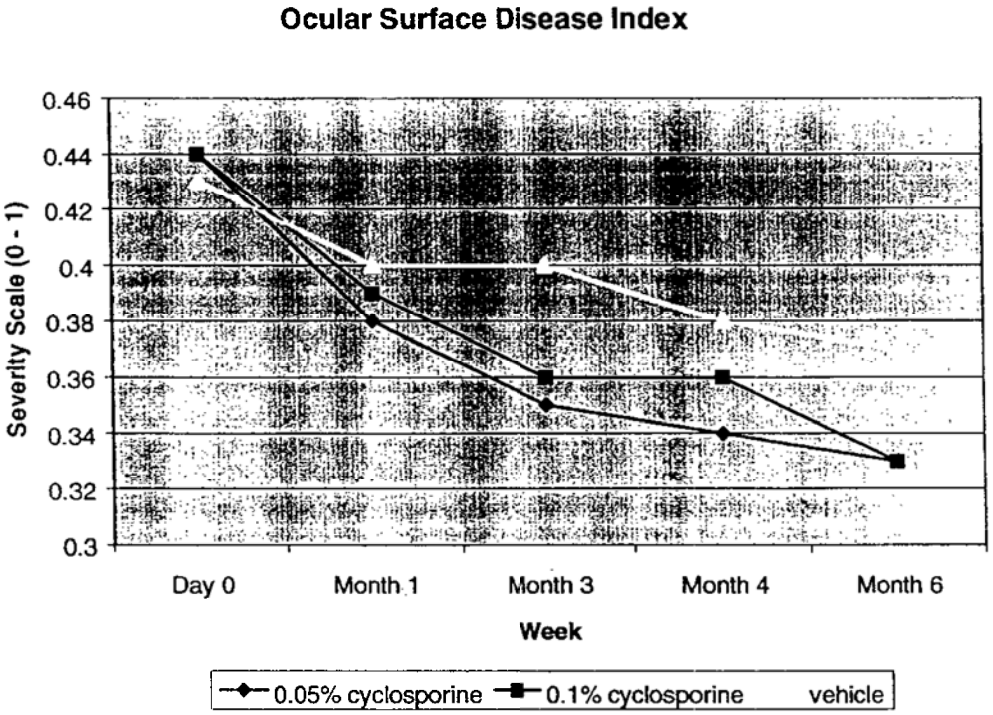
Composite Score - Symptom Severity



Reviewer's Comments:

Composite Symptom Score

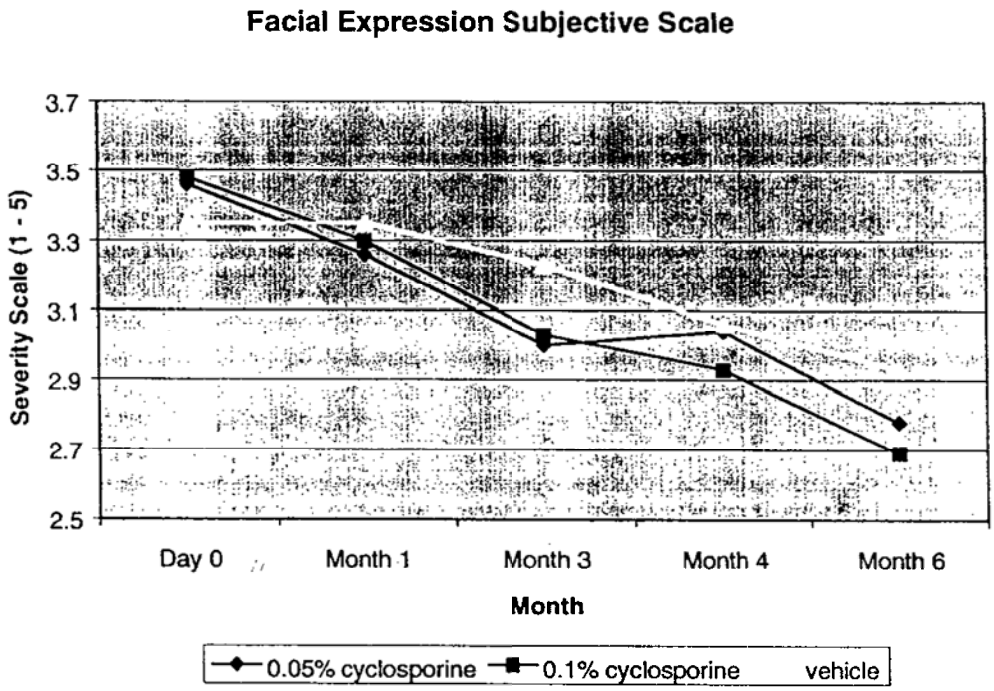
A negative change from baseline indicates improvement.
There are statistically significant improvements from baseline in each treatment group at each visit.
There are statistically significant among-group differences at months 3 and 6, favoring both 0.05% and 0.1% cyclosporine over vehicle (p = 0.024, 0.008).



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).



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

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8.1.1 Safety

Visual Acuity

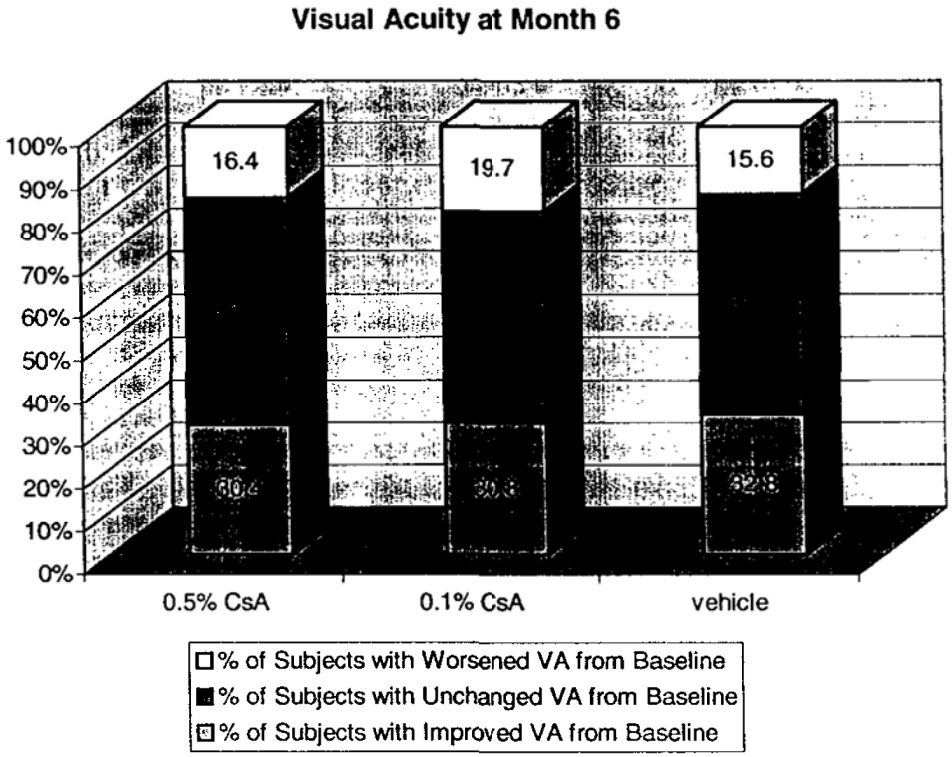

Table 7
Worsening of Baseline VA by More than 3 Lines

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 [redacted] 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 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

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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%	Cyclosporine 0.1%	
[redacted]	1052	1	1	1	422, 423, 425
[redacted]	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%	Cyclosporine 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%	Cyclosporine 0.1%	
[redacted]	2704	10	9	9	101-115; 218; 353-361; 389-391
[redacted]	1438	10	9	10	521-532; 560-571; 590-594
[redacted]	1634	Same as above	Same as above	Same as above	Same as above
[redacted]	1734	11	12	12	128; 144-148; 173-187; 329-330; 380-388; 437-439
[redacted]	2821	4	5	4	533-544; 587
[redacted]	1485	15	15	15	260-268; 344-352; 467-487; 575-577; 584-586
[redacted]	1796	7	9	8	129-137; 230-244
[redacted]	1272	5	5	4	272-276; 284-292

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

Period	Tear *Osmo*[b]	Schirmer *without* Anes	Hx	Preg Test	Subj Asses	VA	TBUT	Corneal Fluores	Interpalp Conjunct Lissamine	Bio	Global	IOP	Schirmer with Anes	Conj Biopsy[b]	Goblet Cell or mRNA[b]	Autoanti-body tests

Schedule of Visits and Measurements (continued)

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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[a]	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
a 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 (ANA, RF, Sjogren A, Sjogren B).

Reviewer's Comments

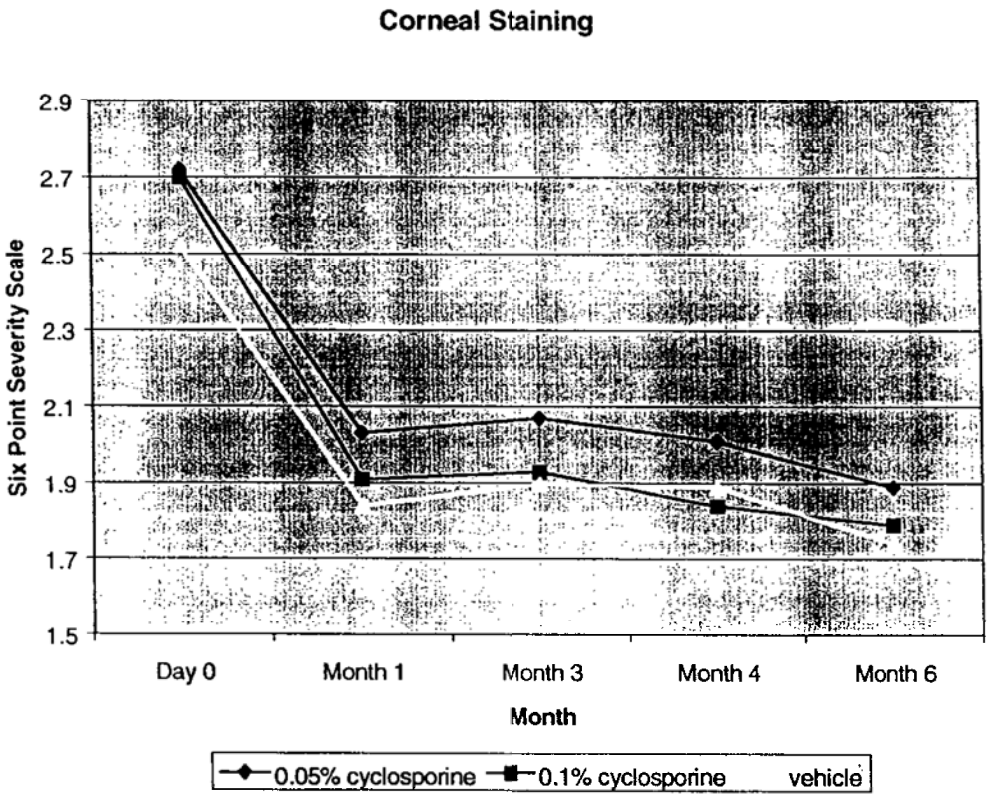
Treatment groups were balanced with respect to age, sex, race, iris color, weight, and height. There were no statistically significant treatment group differences or treatment-by-investigator interactions for these demographic categories.

8.1.2 Efficacy – Objective Signs and Subjective Symptoms

Reviewer's Comments:

Intent-to-treat population unless noted.

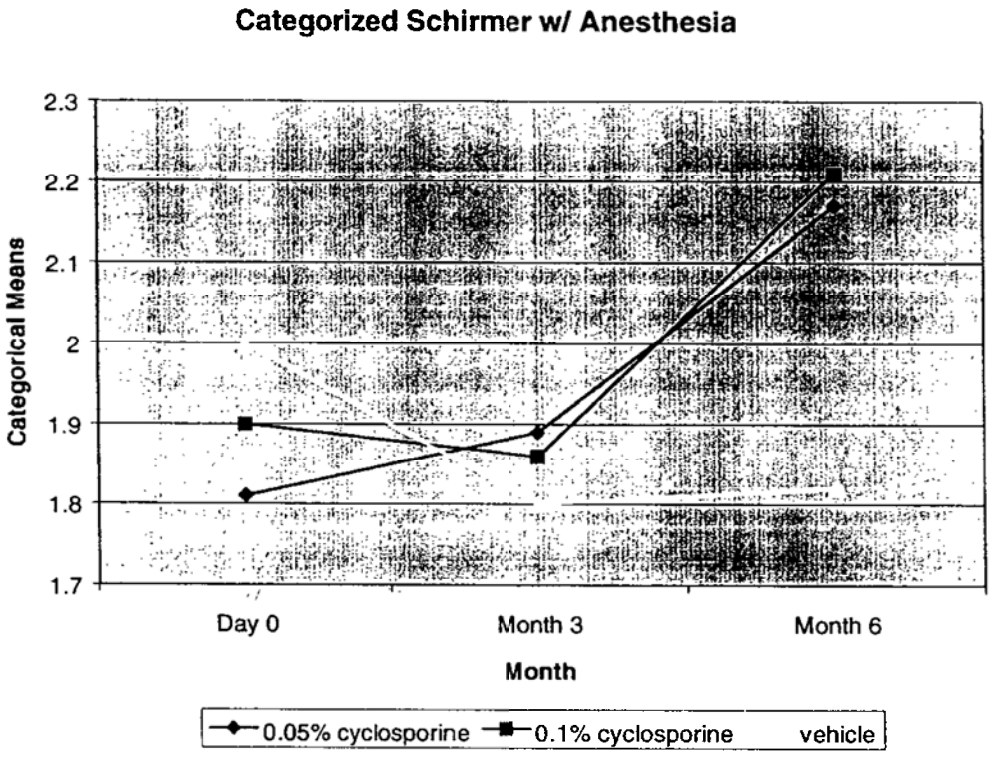
Objective Signs



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.



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

For TBUT 10 seconds, the number of patients is tabulated.
For TBUT < 10 seconds, the three measurements have been averaged for the worse eye.

Reviewer's Comments:

Other Objective Signs

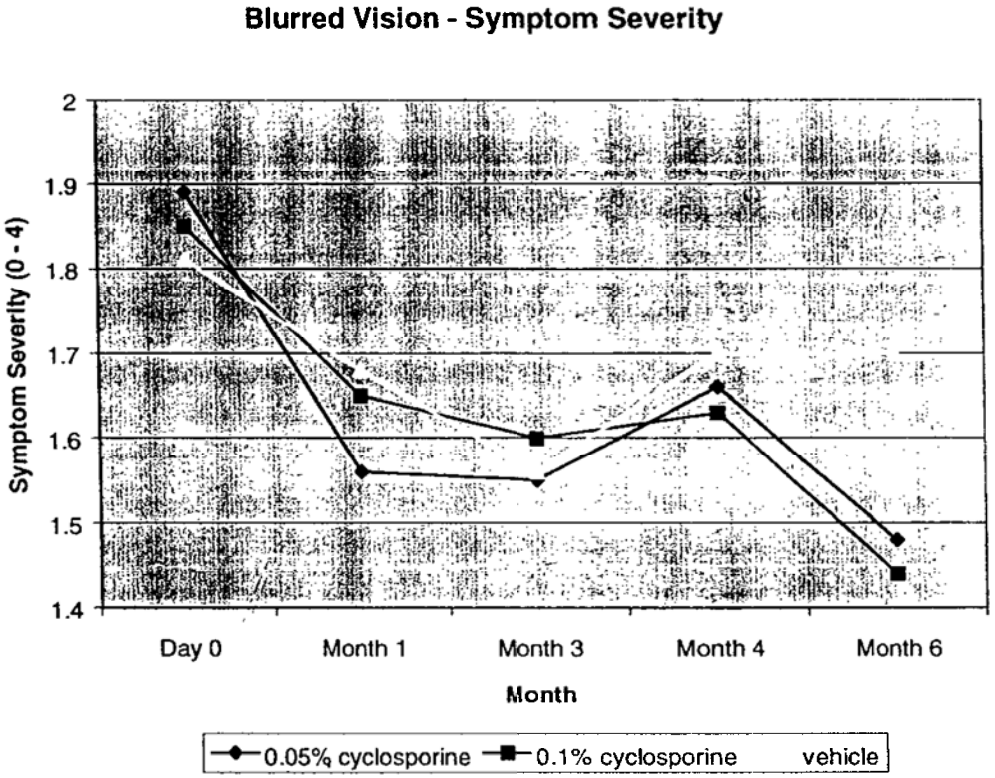
There are no statistically significant among-group differences found for 1)

erpalpebral conjunctival or 4) categorized Schirmer values without anesthesia.

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

, or 4) categorized Schirmer values without anesthesia.

Subjective Symptoms

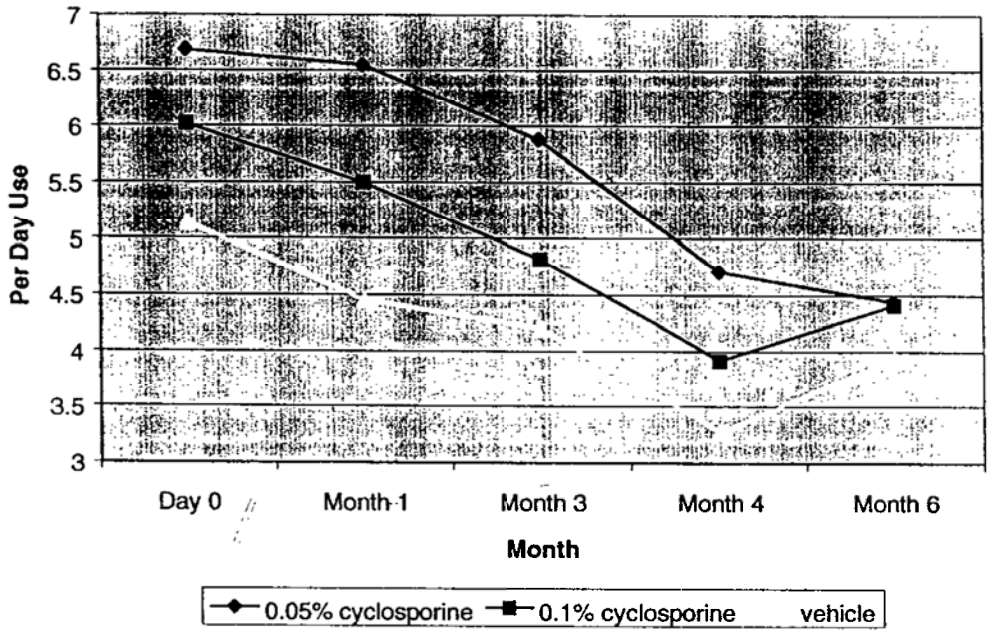


Reviewer's Comments:

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

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=136)		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	(16.3%)	
	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 6								
	N	150		148		147		0.295
	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		0.964
	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

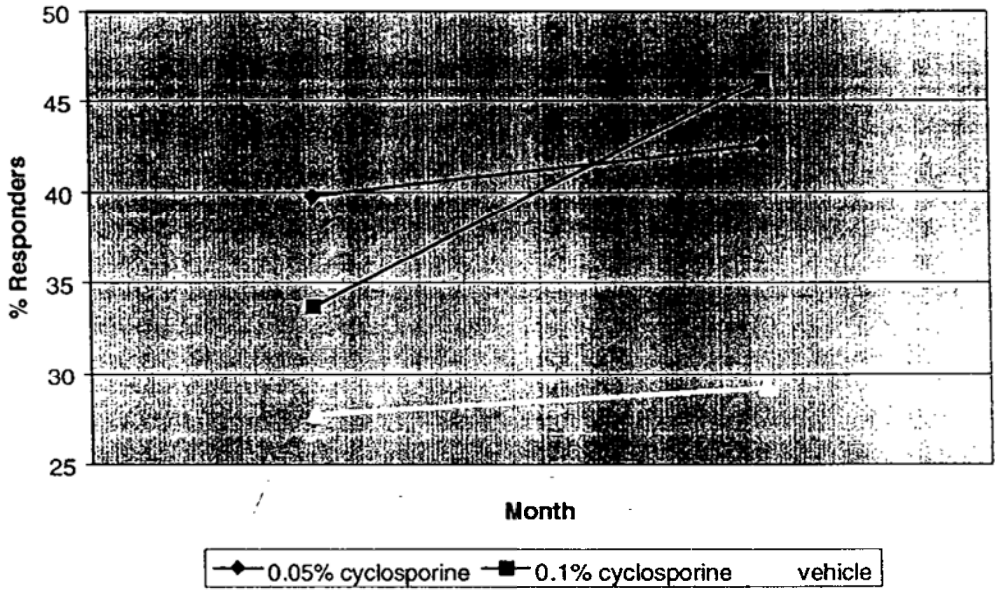
There were no statistically significant differences among the treatment groups at baseline for any of the symptoms except burning/stinging, where the mean for the 0.05% cyclosporine group was significantly higher than for vehicle (respectively, 2.32 and 2.01; p = 0.050).

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 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

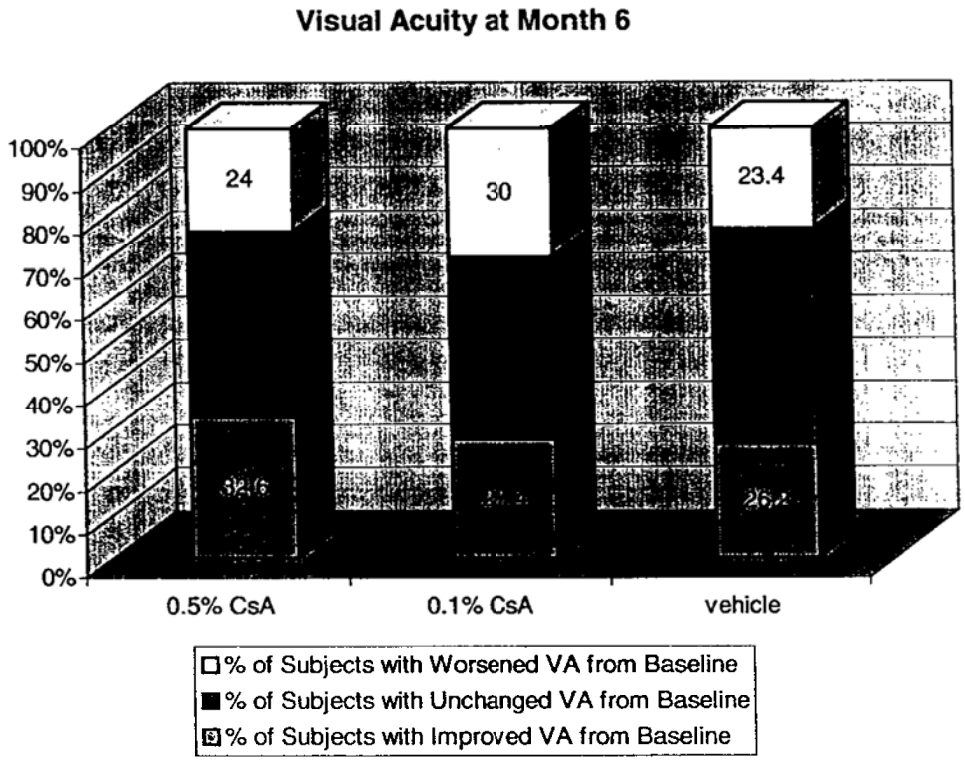


Table 14
Worsening of Baseline VA by More than 3 Lines

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. There

Biomicroscopy

Changes in biomicroscopic findings [redacted] 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 tear film debris 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.

[redacted]

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 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. [redacted]

[redacted]

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.

4 Page(s) Withheld

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
[redacted]	(0200)	13 subjects
[redacted]	(0470)	13 subjects
[redacted]	(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
- [redacted]
- 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) : [redacted]
  2) If Schirmer (without anesthesia) is [redacted] Schirmer with nasal stimulation ≥ [redacted]

- Corneal punctate fluorescein staining ≥ [redacted]
- 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:

  [redacted]

  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 [redacted]

  1) Schirmer (without anesthesia) : [redacted]
  2) If Schirmer (without anesthesia) is [redacted] Schirmer with nasal stimulation [redacted]

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

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

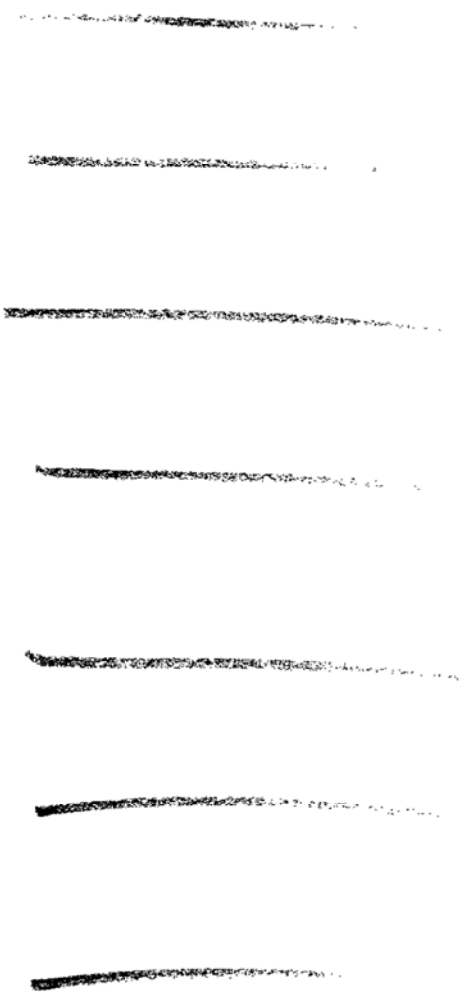
Efficacy Criteria:

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

Secondary efficacy measures were tear film debris, rose bengal staining (RBS), tear breakup time (TBUT), brush cytology, tear meniscus, meibomian glad health, tear proteins, facial expression subjective rating scale, Ocular Surface Disease Index© (OSDI©), Refresh® use, and treatment success (investigator's global evaluation of response to treatment).

Variables assessed by investigators at screening, baseline, and appropriate follow-up visits. Subjective variables reported at scheduled visits and in weekly diaries. Global evaluation evaluated only at follow-up visits.

Efficacy Measures:



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.

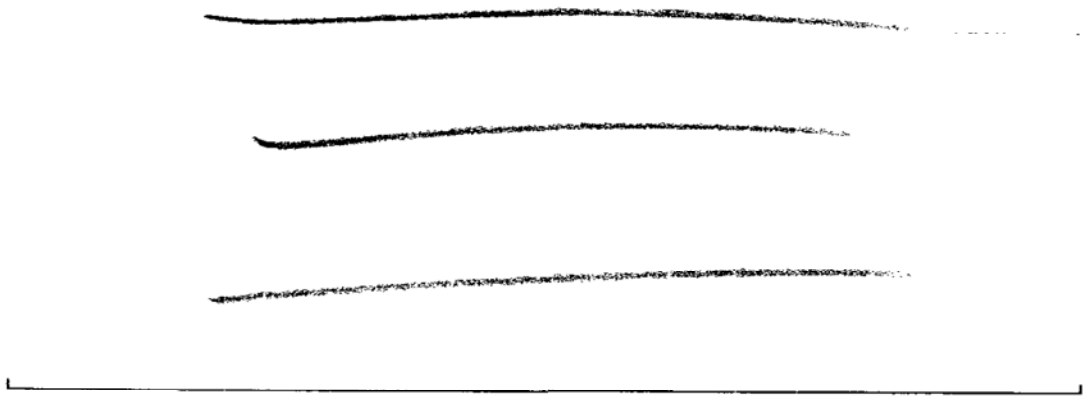


Table 21
Demographics – Age, Race, Sex, Eye Color
ITT Population

Parameter	Vehicle	Cyclosporine 0.05%	Cyclosporine 0.1%	Cyclosporine 0.2%	Cyclosporine 0.4%	Total
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.

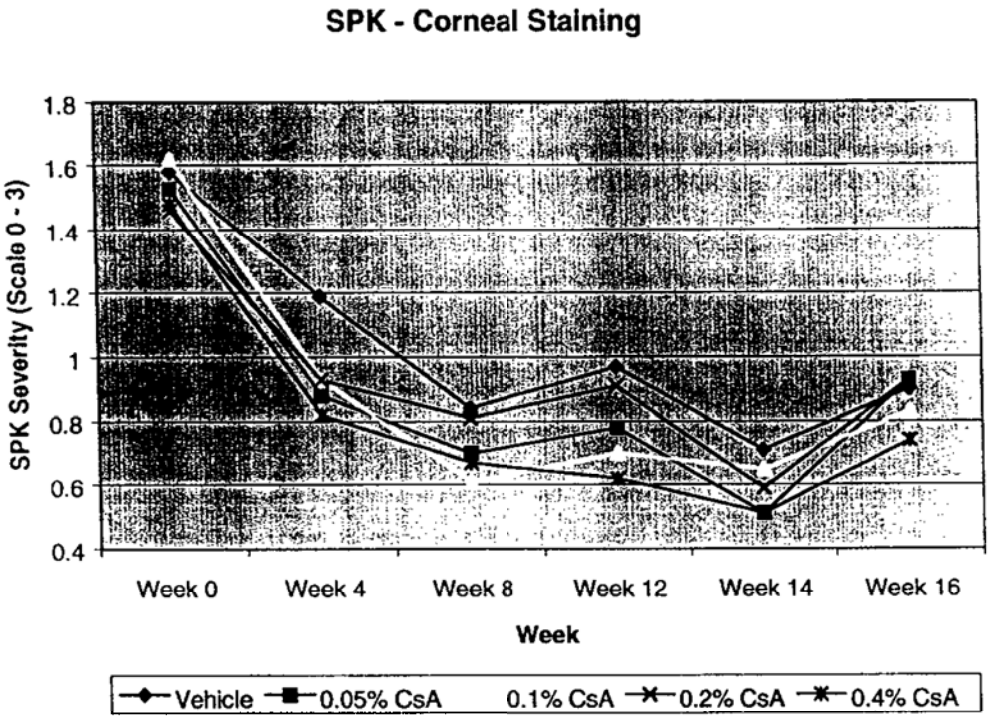
APPEARS THIS WAY
ON ORIGINAL

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.

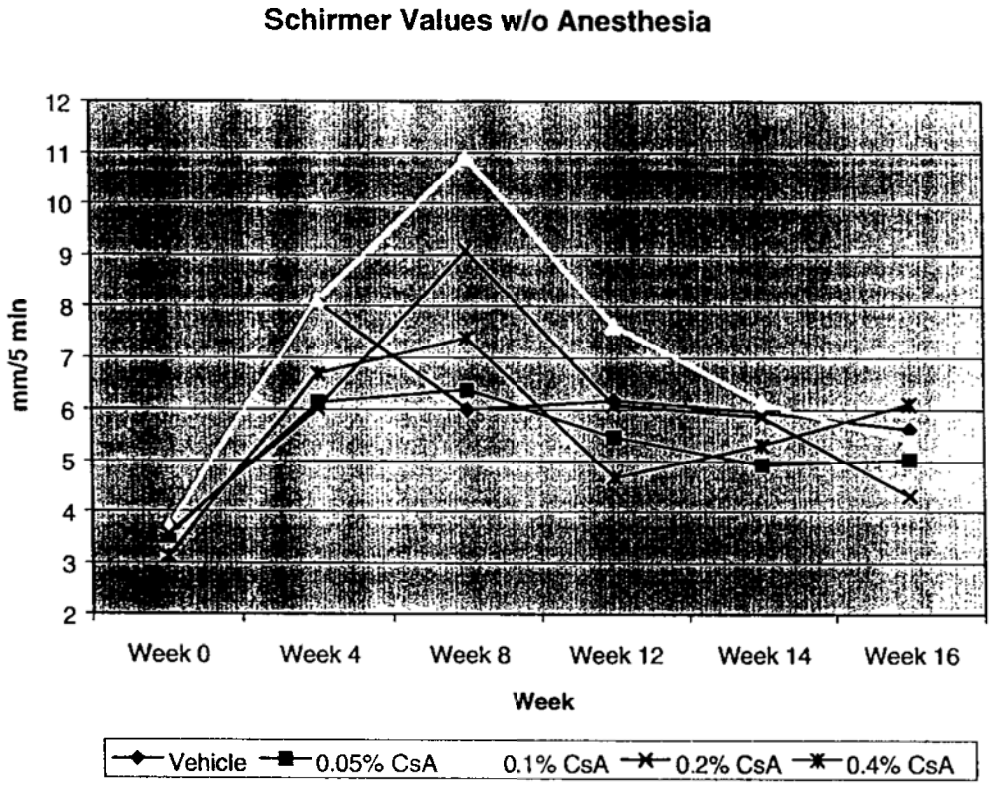
Primary Efficacy Measures



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.

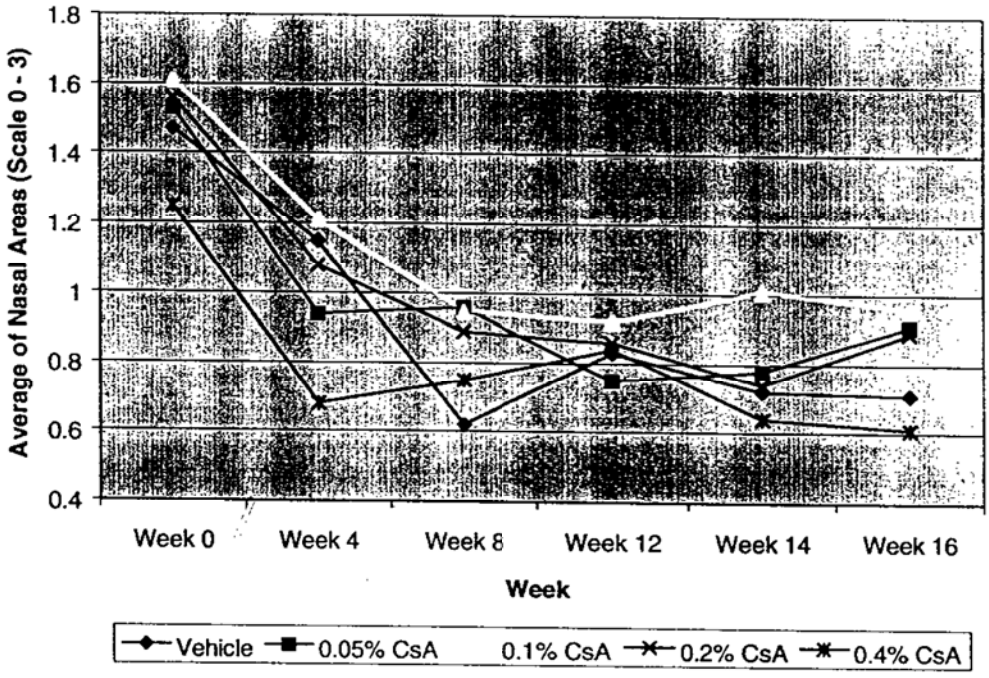


Reviewer's Comments

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.

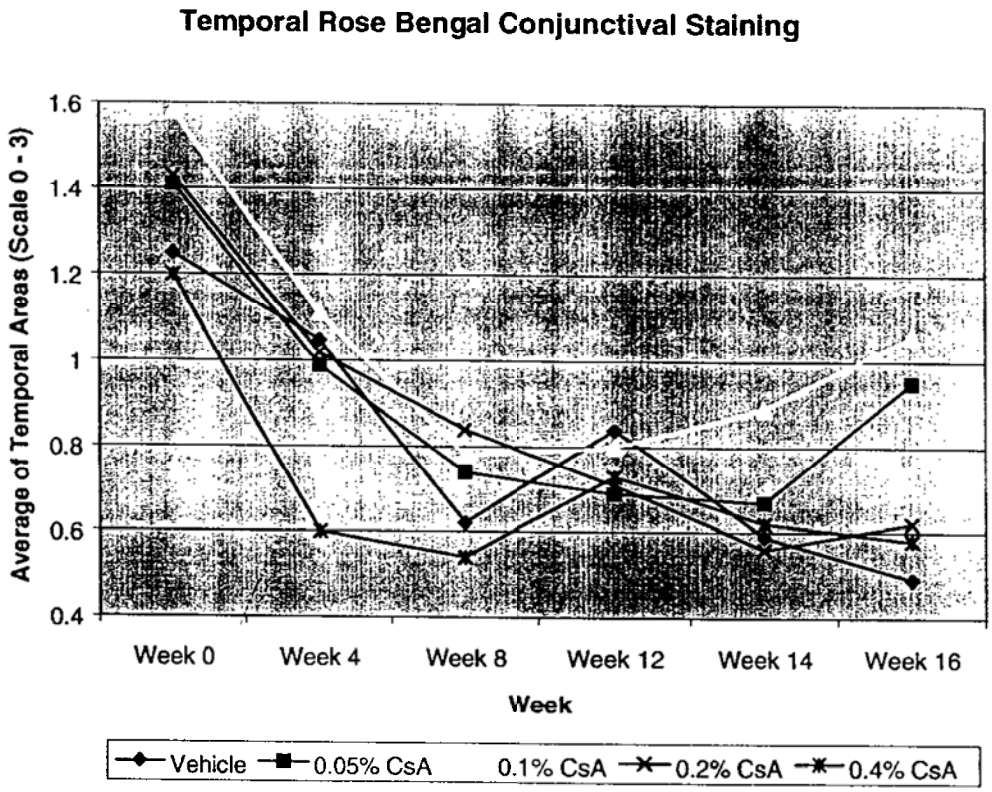
Nasal Rose Bengal Conjunctival Staining



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.

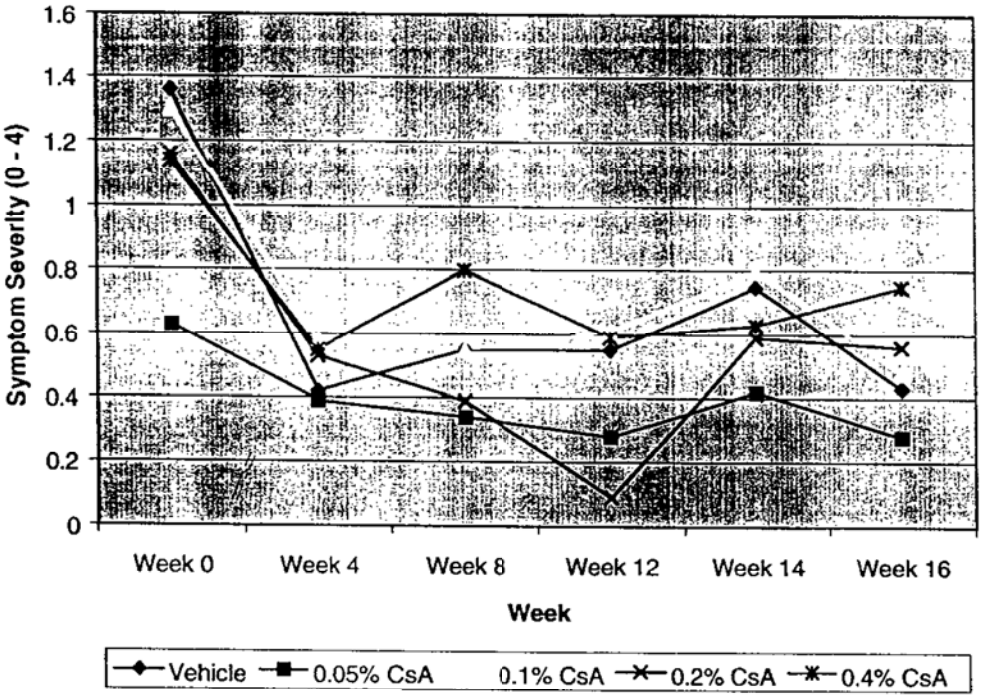


Reviewer's Comments:

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)

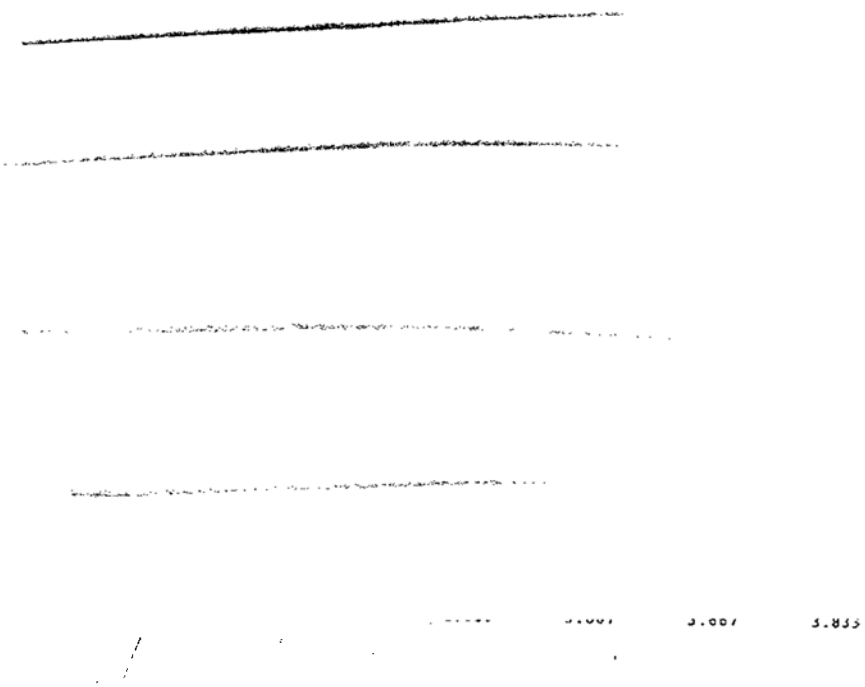
A negative change from baseline indicates improvement.
There are statistically significant improvements from baseline in the vehicle, 0.05%, 0.1%, and 0.2% cyclosporine groups at weeks 4,8, and 12.
There is a statistically significant among-group difference at week 12, favoring 0. 2% cyclosporine over 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 that 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.

[redacted]

Biomicroscopy

Biomicroscopy examination fo[redacted] 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

[redacted]

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 [redacted] suggests no substantial accumulation following multiple ocular dosing for 12 weeks.

Peak whole blood concentration ($C_{max\ 1\text{-}4h}$) of cyclosporine ranged from less than 0.1 ng/ml to [redacted] g/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

[redacted]

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 Sum of Corneal and Interpalpebral Conjunctival 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 two objective signs 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 [redacted] 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.

Summary

On July 21, 1999, NDA 21-073 was referred to the Ophthalmic Drugs Subcommittee of the Dermatologic and Ophthalmic Drugs Advisory Committee for discussion of 0.05% cyclosporine ophthalmic emulsion's use in the treatment of moderate to severe keratoconjunctivitis sicca.

The Subcommittee voted unanimously that efficacy had not been adequately demonstrated in the submitted clinical studies. Recommendations were made to the sponsor to submit one-year efficacy data for Protocols -002 and -003 to the Agency when available. Also, the sponsor may wish to review its clinical data for populations of subjects where efficacy was adequately demonstrated.

The Subcommittee voted unanimously that safety had been adequately demonstrated in the submitted clinical studies

5 Draft Labeling Page(s) Withheld

12 Conclusions

The submitted studies in NDA 21-023 are sufficient to establish the safety of 0.05% cyclosporine ophthalmic emulsion in the treatment of moderate to severe keratoconjunctivitis sicca.

The submitted studies in NDA 21-023 are not sufficient to establish efficacy in the treatment of moderate to severe keratoconjunctivitis sicca. Protocols -002 and -003 are not replicative.

13 Recommendations

The sponsor should submit additional information to support the efficacy of 0.05% cyclosporine ophthalmic emulsion in the treatment of moderate to severe keratoconjunctivitis sicca.

/S/

William M. Boyd, M.D.
Medical Officer

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

Medical Officer's Review of NDA 21-023
120-Day Safety Update

NDA 21-023
Medical Officer's Review

Submission: 7/9/99
Review Completed: 7/27/99

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: Immunomodulator

Proposed Indication: [redacted]

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

Submitted: 120-Day Safety Information for Protocols 192371-002 and 192371-003

Reviewer's Comments and Conclusions:

Numbers of Subjects as Presented in the Data Listings

Protocol 192371-002				
0.05% CsA	**0. 1% CsA**	**0.1% CsA 6 mo. [a]**	**Vehicle [b]**	**Total**
N = 135	N = 134	N = 90	N = 136	N = 405

Protocol 192371-003				
0.05% CsA	**0. 1% CsA**	**0.1% CsA 6 mo. [a]**	**Vehicle [b]**	**Total**
N = 158	N = 158	N = 121	N = 156	N = 472

[a] adverse events from months 6-12 for patients who received vehicle in 1st 6 months of study
[b] adverse events from months 1-6 for patients who received vehicle in 1st 6 months of study

Information contained in this safety update is comparable to previous safety information reviewed for the original NDA.

Original conclusions regarding the safety of 0.05% cyclosporine ophthalmic emulsion in are not altered.

LS

William M. Boyd, M.D.
Medical Officer

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

Medical Officer's Review of NDA 21-023
Major Multidiscipline Amendment

NDA 21-023
Medical Officer's Review

Submission: 12/9/99
Review Completed: 3/9/00

Proposed Tradename: Restasis

Generic Name: Cyclosporine ophthalmic emulsion, 0.05%

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

Pharmacologic Category: Immunomodulator

Proposed Indication: [redacted]

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

Submitted: Major Multidiscipline Amendment
[Response to items identified in the approvable letter dated August 3, 1999]

Sponsor's Clinical Response Overview:

To demonstrate that studies 192371-002 and -003 are replicative and that 0.05% cyclosporine ophthalmic emulsion is effective, this response presents study data from a subpopulation of patients whose dry-eye disease was inadequately controlled with tear substitutes.

To demonstrate replication in the 2 Phase 3 studies and the efficacy of 0.05% cyclosporine emulsion, Allergan has performed new analyses beyond the 6-month ITT analyses submitted in NDA 21-023. A clinically relevant subpopulation of patients whose KCS (keratoconjunctivitis sicca) was inadequately controlled with tear substitutes was defined. The 6-month analyses for these patients demonstrated efficacy in both of the Phase 3 studies. Specifically, there were statistically significant improvements in a clinically relevant sign (categorized Schirmer with anesthesia) and a clinically relevant

symptom (blurred vision) that were replicated in both studies. The proposed labeling for the drug has been revised to reflect its indication for [redacted]

Description of Patients with KCS Inadequately Controlled with Tear Substitutes:

A clinically relevant subpopulation of patients with KCS inadequately controlled with tear substitutes was defined based on a criterion regarding use at baseline of [redacted] tear substitute and 3 key protocol inclusion criteria. These patients met all of the criteria summarized below:

- Patient was using ≥ 4 units of [redacted] tear substitute per day at baseline (day 0).
- Schirmer tear test without anesthesia was ≤ 5 mm/5 min in at least 1 eye.
- The sum of corneal and interpalpebral conjunctival staining was ≥ +5 in the same eye where corneal staining was ≥ +2 and Schirmer was ≤ 5 mm/5 min.
- On the Ocular Surface Disease Index© (OSDI©) questionnaire, patients had a minimum baseline score and answered at least 9 of the 12 questions.

The attributes selected for this subpopulation, as well as the severity of these attributes, describe a population with more severe KCS than the ITT population.

Table 1 - Numbers of Patients with KCS Inadequately Controlled with Tear Substitutes and in the Intent-to-Treat Population

Treatment Group	Study 192371-002		Study 192371-003	
	Subpopulation	Intent-to-Treat	Subpopulation	Intent-to-Treat
0.05% Cyclosporine	72	135	104	158
0.1% Cyclosporine	72	134	103	158
Vehicle	74	136	86	156

Across both studies, 511 (58%) of the original 877 ITT patients were retained in the subpopulation of patients with KCS inadequately controlled with tear substitutes. This subpopulation included more than half of the patients enrolled in each study.

Reviewer's Comments:

Although selected post-hoc, the selection of this subpopulation of patients and the resultant analysis are not fundamentally flawed. The selection criteria used to describe the subpopulation are sound, reasonable, and relevant clinically.

Statistical Methods:

A subgroup analysis was performed for patients with KCS inadequately controlled with tear substitutes as defined previously. As described in NDA 21-023, the last observation

carried forward was used to impute missing data and for efficacy variables collected on both eyes, a "worse" eye was selected.

Efficacy data were summarized with descriptive statistics (i.e., sample size, mean, standard deviation [SD], minimum, maximum, and median). A one-way analysis of variance (ANOVA) with main effect of treatment group was used to test for differences at month 6 in change from baseline among treatment groups. To adjust for multiple comparisons among the 3 treatment groups, if the test for among-group difference for the main effect was significant, then all 3 pairwise comparisons were made. Within-group changes from baseline were analyzed by the paired t-test method. As month 6 has been identified as the primary time point, only the month-6 results are presented here.

Clinically and Statistically Significant Findings at Month 6 Common to Both Studies in Patients with KCS Inadequately Controlled with Tear Substitutes:

Categorized Schirmer Tear Test with Anesthesia

Categorized Schirmer values from grade 1 (< 3 mm/5 min) to grade 5 (≥ 15 mm/5 min) were analyzed (a positive change from baseline indicates improvement). Results of the Schirmer tear test with anesthesia are summarized for the patients with KCS inadequately controlled with tear substitutes by study in Table 2.

Table 2 - Categorized Schirmer Values with Anesthesia at Baseline and Change from Baseline at Month 6 in Patients with KCS Inadequately Controlled by Tear Substitutes

	Mean ± Standard Deviation (N)					
	Study 192371-002			Study 192371-003		
	CsA 0.05%	CsA 0.1%	Vehicle	CsA 0.05%	CsA 0.1%	Vehicle
Day 0	1.96 ± 0.91 (72)	2.31 ± 1.16 (72)	2.12 ± 0.98 (74)	1.64 ± 0.82 (102)	1.87 ± 0.93 (99)	2.01 ± 1.05 (84)
Among-group p-value	0.127			0.022[a]		
Change from baseline:						
Month 6	0.76 ± 1.39 (66)	0.24 ± 1.15 (62)	0.29 ± 1.22 (62)	0.56 ± 1.23 (91)	0.61 ± 1.18 (83)	-0.01 ± 0.98 (77)
Within-group p-value	< 0.001	0.104	0.066	< 0.001	< 0.001	0.908
Among-group p-value	0.040			< 0.001		
P-value for pairwise comparisons vs. vehicle	0.046	0.821	NA	0.001	< 0.001	NA

Note: CsA = cyclosporine ophthalmic emulsion, NA = not applicable. Schirmer values categorized as 1 (< 3 mm/5 min), 2 (3 to 6 mm/5 min), 3 (7 to 10 mm/5 min), 4 (11 to 14 mm/5 min), and 5 (≥ 15 mm/5 min) using the worse eye. A positive change indicates improvement.

a At day 0, patients randomized to vehicle had significantly higher (i.e., less severe) Schirmer values than patients randomized to 0.05% cyclosporine ophthalmic emulsion (p=0.007).

In study 002 at month 6, the within-group comparisons showed a statistically significant improvement from baseline with 0.05% cyclosporine but not with 0.1% cyclosporine or vehicle. The among-group difference was statistically significant ($p = 0.040$). The pairwise comparison for 0.05% cyclosporine vs. vehicle showed a statistically significant difference in favor of 0.05% cyclosporine ($p = 0.046$).

In study 003 at month 6, the within-group comparisons showed statistically significant improvements from baseline with both concentrations of cyclosporine, in contrast to essentially no change in the vehicle group. The among-group difference was statistically significant ($p < 0.001$). Pairwise comparisons for 0.05% cyclosporine vs. vehicle and 0.1% cyclosporine vs. vehicle showed statistically significant differences in favor of cyclosporine ($p \leq 0.001$).

Because there was a significant difference among treatment groups at day 0 in study 003, an analysis of covariance (ANCOVA), using the baseline value as covariate, was performed to examine treatment differences at month 6. Results from the ANCOVA did not change the conclusion that 0.05% cyclosporine was statistically significantly better than vehicle at month 6.

Blurred Vision

A 5-grade subjective scale was used to assess blurred vision with scores ranging from "I do not have this symptom" (0) to "I always notice this symptom, it does make me uncomfortable, it does interfere with my activities" (+4) (a negative change from baseline indicates improvement). Results for blurred vision are summarized for the patients with KCS inadequately controlled with tear substitutes by study in Table 3.

Table 3 - Blurred Vision at Baseline and Change from Baseline at Month 6 in Patients with KCS Inadequately Controlled by Tear Substitutes

	Mean ± Standard Deviation (N)					
	Study 192371-002			Study 192371-003		
	CsA 0.05%	CsA 0.1%	Vehicle	CsA 0.05%	CsA 0.1%	Vehicle
Day 0	2.31 ± 1.38 (72)	1.97 ± 1.30 (72)	1.86 ± 1.24 (74)	1.99 ± 1.30 (104)	1.92 ± 1.32 (103)	1.97 ± 1.32 (86)
Among-group p-value	0.109			0.932		
Change from baseline:						
Month 6	-0.50 ± 1.50 (70)	-0.41 ± 1.15 (69)	-0.01 ± 1.01 (72)	-0.46 ± 1.18 (100)	-0.49 ± 1.23 (97)	-0.01 ± 1.36 (82)
Within-group p-value	0.007	0.005	0.908	< 0.001	< 0.001	0.935
Among-group p-value	0.048			0.019		
P-value for pairwise comparisons vs vehicle	0.025	0.034	NA	0.018	0.013	NA

Note: CsA = cyclosporine ophthalmic emulsion, NA = not applicable. Blurred vision was measured on a scale from 0 (do not have symptom) to 4 (always notice this symptom). A negative change indicates improvement.

In both studies at month 6, the within-group comparisons for both cyclosporine concentrations showed statistically significant improvements of approximately 0.5 grade from baseline. In contrast, vehicle-treated patients showed essentially no change. The among-group difference was statistically significant in each study ($p \leq 0.048$). Pairwise comparisons for 0.05% cyclosporine vs. vehicle and 0.1% cyclosporine vs. vehicle showed statistically significant differences in favor of cyclosporine ($p \leq 0.034$).

Reviewer's Comments:

1) *There are multiple [five (5) subjective and five (5) objective] endpoints specified in the original NDA, and the p-values presented for Categorized Schirmer w/ Anesthesia and Blurred Vision in this Amendment are not corrected for multiplicity.*

2) *The statistically significant p-values for pairwise comparisons of 0.05% cyclosporine vs. vehicle in Studies 192371-002 and 192371-003 are calculated using change-from-baseline values.*

   When p-values are calculated (1-way Analysis of Variance) with the actual given means by visit at Month 6, the resultant values do not demonstrate statistical significance favoring 0.05% cyclosporine over vehicle. See Tables 4 and 5 below for Categorized Schirmer Values with Anesthesia and Blurred Vision.

Table 4 - Categorized Schirmer Values with Anesthesia at Baseline and at Month 6 in Patients with KCS Inadequately Controlled by Tear Substitutes

	Means by Visit					
	Study 192371-002			Study 192371-003		
	CsA 0.05%	CsA 0.1%	Vehicle	CsA 0.05%	CsA 0.1%	Vehicle
Day 0	1.97 (66)	2.31 (62)	2.00 (62)	1.63 (91)	1.81 (83)	1.97 (77)
Among-group p-value	0.113			0.052		
Month 6	2.73 (66)	2.55 (62)	2.29 (62)	2.19 (91)	2.42 (83)	1.96 (77)
Within-group p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Among-group p-value	0.149			0.057		
P-value for pairwise comparisons vs. vehicle	0.053	0.229	NA	0.208	0.013	NA

Note: CsA = cyclosporine ophthalmic emulsion, NA = not applicable. Schirmer values categorized as 1 (< 3 mm/5 min), 2 (3 to 6 mm/5 min), 3 (7 to 10 mm/5 min), 4 (11 to 14 mm/5 min), and 5 (≥ 15 mm/5 min) using the worse eye. Day 0 values are provided only for patients with month 6 data.

Table 5 - Blurred Vision at Baseline and at Month 6 in Patients with KCS Inadequately Controlled by Tear Substitutes

	Means by Visit					
	Study 192371-002			Study 192371-003		
	CsA 0.05%	CsA 0.1%	Vehicle	CsA 0.05%	CsA 0.1%	Vehicle
Day 0	2.29 (70)	2.04 (69)	1.90 (72)	2.02 (100)	1.39 (97)	1.93 (82)
Among-group p-value	0.210			0.767		
Month 6	1.79 (70)	1.64 (69)	1.89 (72)	1.56 (100)	1.39 (97)	1.91 (82)
Within-group p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Among-group p-value	0.543			0.022		
P-value for pairwise comparisons vs. vehicle	0.656	0.267	NA	0.066	0.007	NA

Note: CsA = cyclosporine ophthalmic emulsion, NA = not applicable. Blurred vision was measured on a scale from 0 (do not have symptom) to 4 (always notice this symptom). Day 0 values are provided only for patients with month 6 data.

Conclusions:

The submitted studies in NDA 21-023 are not sufficient to establish efficacy in the

Studies 192371-002 and 192371-003 are not replicative.

Recommendations:

The sponsor should submit additional information to support the efficacy of 0.05% cyclosporine ophthalmic emulsion

/S/

William M. Boyd, M.D.
Medical Officer

NDA 21-023
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HFD-550/PM/Gorski
HFD-340/Carreras
HFD-550/PharmTox/Mukherjee

/S/