CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-023

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-023 SUBMISSION DATE: 2/25/99, 3/30/99

PRODUCT: Restatis™ 0.05%
(Cyclosporin Ophthalmic Emulsion)

SPONSOR: Allergan, Inc.
Irvine, CA.

REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

I. Background

Cyclosporine ophthalmic emulsion 0.05% is indicated for [redacted]. It acts as an immunomodulator and an anti-inflammatory agent. Cyclosporin helps in suppressing the immune-based inflammation of the ocular surface, allowing for the secretion of more normal ocular surface supportive tears and a more stable tear film. Topical use of cyclosporin exerts a local effect only, an action termed immunomodulatory, rather than systemic immonosuppresive effect. Although cyclosporin is not a classical anti-inflammatory agent and has not been demonstrated to inhibit cyclo-oxygenase, it does inhibit inflammation in other ways. Cyclosporine prevents the synthesis and/or secretion of several TH1 pro-inflammatory cytokines, and is also known to upregulate secretion of TH2-type anti-inflammatory cytokines. Additionally, cyclosporine has been shown to regulate immune-based inflammation within ocular surface tissues by inhibiting intercellular adhesion molecule-1 (ICAM-1).

Current treatment options for dry eye are palliative, and provide symptomatic relief only without addressing the underlying mechanisms of the disease. Cyclosporine, as an immunomodulating agent, has been shown to break the cycle of the immune reactivity underlying the disease both in dry-eye dogs[1,2] and in dry-eye patients[3]. Cyclosporine reduces lacrimal gland lymphocytic infiltrates and improves tear production in KCS dogs [1,4,5] and in KCS patients with or without Sjögren's syndrome [2,3,6,7]. Power et al demonstrated that patients with secondary Sjögren's disease are undergoing continued

[1] Kaswan et al, Arch ophthalmol, 107:1210-1216, 1989
[2] Stern at al, Cornea, 17:584-589,1998
[3] Power et al, Cornea,12:507-511,1993
[4] Kaswan et al, Vet Clin North Am Small Anim prac, 20:583-613,1990
[5] Morgan et al, J Am Vet Assoc, 199:1043-1046, 1991
[6] Drosos el al, Ann Rheum Dis, 45:732-735,1986
[7] Laibovitz et al, Cornea, 12:315-323,1993

immune reactivity, indicated by the presence of significantly more CD4 (T-helper) cells than age/sex-matched controls. Following treatment with topical cyclosporine, there was a significant reduction in the number of CD4 cells in both the conjunctival epithelium and substantia propria, indicating immunopathological improvement.

Oral cyclosporin is available for the treatment of rheumatoid arthritis, psoriasis (2.5 to 5 mg/kg/day-NEORAL®) and systemic prophylaxis of organ transplant rejection (7-9 mg/kg/day-NEORAL®). SANDIMMUNE® is also used at higher doses, but has lower bioavailability as compared to NEORAL®. In contrast topical cyclosporin emulsion is to be used at the dose of 1 to 2 μg/kg/day.

Dosage and Administration
The recommended dosage is one drop (—) of RESTASIS™ (0.05%) instilled twice a day in each eye approximately 12 hours apart.
Foreign marketing history
Not yet marketed in any other country.

II. Recommendation

The cyclosporin concentrations were below the limit of quantitation in most samples. Only 9 samples out of 348 samples from the phase 2 and 3 studies had quantifiable concentrations, with a highest value of — ng/ml. All these samples were from patients receiving 0.1% cyclosporin emulsion. The C_{max}, C_{min} and AUC_{0-12} were several orders of magnitude below than those produced by systemic treatments already approved for non-life threatening conditions. All patients treated with 0.05% cyclosporin emulsion, were below the detection limit of 0.1 ng/ml with up to 9 months of dosing.

The concentration-time profile of cyclosporin in tears over the course of one 12 hour dosing interval and the 12 month data from study 192371-002 has not been submitted yet. The application is approvable from the biopharmaceutics standpoint, contingent upon the availability of the remaining data and its appropriateness.

CONTENTS

III. Formulation

Ingredient	Concentration for 0.05% (%w/w) To-be marketed	Concentration for 0.1%% (%w/w) Not-to-be marketed
Cyclosporin USP	0.05	0.1
Castor oil PhEur		
Glycerine USP		
Polysorbate 80 NF		
Carbomer 1324 nF		
Sodium hydroxide NF		
Purified water USP		

IV. Analytical Validation

Cyclosporin A in human blood was analyzed using [redacted] and

LOQ: 0.1 ng/ml

Linearity: The linearity was tested over the concentration range [redacted] with a coefficient of correlation of [redacted] for day [redacted] of the validation, respectively.

Intra-day Precision and Accuracy: The accuracy of intra-day variability ranged from [redacted] of the nominal concentrations and precision (%CV) ranged from [redacted]

Inter-day Precision and Accuracy: The accuracy ranged from [redacted] of the nominal with a precision between [redacted]

Freeze-Thaw Stability: The mean percent differences from nominal were [redacted] at [redacted] respectively after [redacted]. The precision was [redacted] and [redacted] at [redacted] respectively.

Stability: At room temperature- Mean percentage difference from nominal was [redacted] after 24 hours and [redacted] after 48 hours for [redacted]. It was [redacted] after 24 hours and [redacted] after 48 hours for [redacted] Precision ranged from [redacted]

After [redacted] - mean percent difference was [redacted] and [redacted] for [redacted] and [redacted] respectively. The precision was [redacted], respectively.

In human blood, unextracted for 24 hours at room temperature- Mean percent difference from nominal was [redacted] and precision was [redacted], respectively.

Recovery: The percent recovery of the overall process which includes [redacted] and [redacted] was [redacted] which is unusually high.

V. Pharmacokinetic Studies

The human pharmacokinetics of cyclosporin ophthalmic emulsion has been evaluated in a phase II dose ranging study and a phase III safety and efficacy study for up to one year duration. Blood samples up to 9 months have been evaluated. The 12th month blood cyclosporin concentrations and concentration-time profile in tears up to 12 hours of dosing will be submitted later.

Quantitation of cyclosporin A was preferred in whole blood over plasma due to high blood-plasma concentrations ratios at very low doses of cyclosporin and even on systemic dosing. Cyclosporin has high affinity of blood cells than for plasma proteins. Preliminary in vitro experiments evaluating the blood-to-plasma concentration ratio suggested that blood concentrations of cyclosporin may be twice those of plasma.

Study # 192371-001 (PK-96-018)

A dose ranging study evaluating the safety, tolerability and efficacy of cyclosprorin (0.05, 0.1, 0.2, 0.4%) and vehicle ophthalmic emulsions in the treatment of moderate to severe keratoconjuctivitis sicca.

This study was a randomized, double-masked, parallel-group design in 162 subjects (26M and 136F) treated topically with either vehicle, 0.05%, 0.1%, 0.2% or 0.4% cyclosporin emulsion twice daily in each eye for 12 weeks.

Blood samples were collected from each subject at baseline, trough samples prior to morning dose following 1, 4, and 12 weeks of dosing. To obtain maximum blood concentrations for each treatment groups, blood samples were also collected at one of the study sites from approximately 3-5 subjects per treatment group at 1, 2 and 4 hours after the final dose at the end of 4 weeks of dosing. Peak blood concentrations are reported to occur between 1 and 4 hours after oral dosing. Blood samples were also collected at 4 weeks post treatment (week 16).

Results

Cyclosporin A was neither quantifiable in blood samples collected prestudy from all subjects nor in blood samples from vehicle-treated subjects after 1, 4 and 12 weeks of dosing. Trough samples after 1, 4 and 12 weeks of dosing with 0.05, 0.1, 0.2, and 0.4% cyclosporin twice daily were very low (less than 0.2 ng/ml). Only 5 out of 120 subjects (includes all dosing groups) showed detectable trough concentrations with values of _____ ng/ml. The ranges of trough blood concentrations for the four treatment groups after 1, 4 and 12 week of dosing and maximum blood concentration at 1, 2 and 4 hours after the last dose on week 12 are shown in the following table.

Treatment group	Trough Conc. at weeks 1, 4, 12 (C_{min})* Range	Maximum Conc. on week 12** $C_{max1-4\ hr}$ Range
0.05%	<0.1 ng/ml	<0.1 ng/ml
0.1%	<0.1 to [redacted] ng/ml[a]	<0.1 ng/ml
0.2%	<0.1 to [redacted] ng/ml[b]	[redacted] ng/ml
0.4%	<0.1 to [redacted] ng/ml[c]	<0.1 to [redacted] ng/ml

*N=120 (28-33 subjects per group) ** N=15 (3-5 subjects per group)
a= highest value at week 1
b= highest value at week 12
c=highest value at week 4

The week 16 blood samples were not analyzed. The individual subject data is attached in the Appendix on pages 10-14.

Conclusions

- Overall, the results demonstrate that ocular instillation of 0.05 to 0.4% cyclosporin emulsion produces low systemic exposure of cyclosporin A. The highest trough concentration was [redacted] ng/mL which was at least 600-fold lower than trough concentrations of 100-400 ng/mL reported after administration of therapeutic oral doses of cyclosporin A to organ transplant patients (Transplant Proceed 20,Suppl 2; 382-389,1985).
- Peak concentration at 1-4 hours post dose on week 12 was [redacted] ng/ml after instillation of 0.4% topical cyclosporin emulsion. Peak blood concentrations after oral administration of each mg of cyclosporin ranged from 1.4 to 2.7 ng/mL at 2 to 4 hours post dosing (Goodman Gilman's, "Pharmacological Basis of Therapeutics", 7th edition, pg 1299).

Reviewer's Comment

Ocular pharmacokinetic studies in rabbits after a single drop of 0.2% cyclosporin indicated a 26 to 44 hour half life in most ocular tissues (Study report PK-95-010, 1995), suggesting the possibility of once daily dosing. However, the sponsor has chosen a twice-daily regimen for the dose ranging study. The sponsor has chosen this regimen to minimize differences between peak and trough drug levels and therefore, provide more constant drug exposure to ocular tissues over the entire dosing interval.

Study # 192371-002 (PK-98-109 and PK-98-112)

A multicenter, double masked, randomized, vehicle conrolled, parallel-group study of safety and efficacy of cyclosporin 0.05% and 0.1% ophthalmic emulsions used twice daily for up to 1 year in patients with moderate to severe keratoconjunctivitis sicca.

Patients were administered either vehicle, 0.05% or 0.1% cyclosporin ophthalmic emulsion. Patients taking vehicle emulsion were switched to 0.1% cyclosporin emulsion

at month 6, therefore, during months 9 to 12, all patients were taking either 0.05 or 0.1% emulsion. Formulations used and their batch numbers are given in Appendix on page 15.

The cyclosporin doses instilled were 0.0570 and 0.114 mg/day during 0.05% and 0.1% treatment groups, assuming a drop volume of 28.5 µl. Cyclosporin was quantified in trough blood samples taken from selected patients before the start of treatment and after 1, 6 and 9 months of treatment. Trough blood concentrations between month 9 and 12 were analyzed at preselected site at 1, 2, 3, 4, 6, 8, 10 and 12 hours after the morning dose.

Trough blood concentration at month 12 and concentration-time profile of cyclosporin A in tears measured during the course of a 12 hour dosing interval will be submitted later.

Results

Month 1 and Month 6

A total of 338 samples from 131 patients were analyzed up to 6 months, consisting of 131 prestudy samples, 113 samples at 1 month and 94 samples at month 6. 140 samples were from cyclosporin treated patients collected at months 1 or 6, out of these 70 were from each 0.05% and 0.1% cyclosporin treatment group.

Mean concentrations in all treatment groups at all sampling times were BLQ. Only 6 out of 140 samples collected from cyclosporin treated patients at months 1 and 6 had quantifiable cyclosporin A concentrations. Out of these 6 patients, there were 5 females and one male. 3 patients each at month 1 and month 6 had quantifiable levels. The concentrations at month 1 were [redacted] and [redacted] ng/ml. Out of these 3, two were BLQ at month 6, and one of them was not analyzed at month 6. The quantifiable concentrations at month 6 were [redacted] and [redacted] ng/ml. All these 3 patients were BLQ at month 1. All the concentrations belonged to the 0.1% cyclosporin emulsion treatment group. The data for these 6 subjects is attached in the Appendix in Table IV and V on page 15.

Month 9

208 post-dose samples were analyzed between 9 and 12 months from 26 patients, 8 on 0.05% and 18 patients on 0.1% cyclosporin emulsion. Out of the 18 taking 0.1%, 9 had taken 0.1% cyclosporin emulsion for 9-12 months and the other 9 were on vehicle till 6 months and then on 0.1% cyclosporin emulsion for another 3-6 months.

AUC_{0-12} was calculated using linear trapezoidal rule. Since most concentrations were BLQ, an upper limit to AUC_{0-12} was calculated assuming a mean Cmax equal to the LOQ at each sampling time and then expressing the mean AUC_{0-12} as below this upper limit.

Mean C_{max} was not calculable but was less than 0.1 ng/ml in 0.05 and 0.1% treatment groups. Out of the 208 post dose samples from 26 pateints, only 3 samples from 3 different patients contained quantifiable concentrations. They were: ——ng/ml at 1 hr, — ng/ml at 2 hrs,—— ng/ml at 3 hrs. This is shown in Table III on page 16 of the Appendix. Concentrations in other 205 samples were below the LOQ of 0.1 ng/ml. The AUC was less than 1.2 ng.hr/ml in both treatment groups.

Conclusions

- The highest trough blood concentration observed was —— ng/ml with the 0.1% emulsion. All concentration values were below 0.1 ng/ml in the 0.05% emulsion group.
- The cyclosporin doses instilled were 0.0570 and 0.114 mg/day during 0.05% and 0.1% treatment groups. Assuming a 60 Kg patient, these doses are 0.000950 mg/kg/day and 0.0190 mg/kg/day. The recommended starting dose of NEORAL® for the treatment of rheumatoid arthritis and psoriasis is 2.5 mg/kg/day to 5 mg/kg/day. The topical doses are 2,630 and 1,320 times lower, than the starting NEORAL® doses. The mean trough blood concentrations after topical cyclosporin emulsions were less than 0.1 ng/ml. The trough concentrations from systemic use ranged from 74.9 to 46.7 ng/ml (PDR-NEORAL, 1998). The trough concentrations after topical use is at least 750 times lower than mean trough levels seen with systemic therapeutic use. The mean Cmax produced by systemic use ranged from 655±186 to 728±265 ng/ml and that after 'topical application of the emulsions were less than 0.1 ng/ml, therefore, at least 6,550 times lower than that produced with systemic use. The blood AUC_{0-12} produced by topical application was less than 1.2 ng.hr/ml, and therefore, at least 1,940 times lower than that produced after oral use.

These comparisons between the 0.05% and 0.1% cyclosporin emulsion and NEORAL® are tabulated below.

Mean parameter	NEORAL®[a]	Cyclosporine ophthalmic emulsions[b]	NEORAL®/ophthalmic emulsion ratio
Starting dose (mg/60 kg/day)	150	0.114 (0.1%) 0.0570 (0.05%)	1,320 (0.1%) 2,630 (0.05%)
C_{max} (ng/mL)[c]	655	<0.1	>6,550
$C_{average}$ (ng/mL)[d]	194	<0.1	>1,940
C_{min} (ng/mL)[e]	74.9	<0.1	>749
AUC_{0-12} (ng hr/mL)[c]	2,324	<1.2	>1,940

[a] blood cyclosporine concentrations measured during oral treatment of rheumatoid arthritis or psoriasis with NEORAL®

[b] blood cyclosporin A concentrations measured during ophthalmic treatment with cyclosporine emulsions

[c] from PDR-NEORAL®, 1998 (for NEORAL®) and study report PK-98-112 (for cyclosporine emulsions)

[d] calculated as AUC_{0-12} (ng•hr/ml)÷12 hr

[e] from PDR-NEORAL®, 1998 (for NEORAL®) and PK-98-109 (for cyclosporine emulsions)

- Comparing to the animal data it was found that blood C_{max} in rabbits and dogs were at least 14 and 7 times higher, respectively, than the blood C_{max} in humans during ophthalmic treatment with cyclosporine emulsions. However, concentrations in these animals were still more than 440 times lower than the mean blood C_{max} produced by approved oral treatment with cyclosporine for systemic indications.

Reviewer's Comment (not for the sponsor)

With these comparisons it is clear that the systemic exposure from 0.05% cyclosporin ophthalmic emulsion is minimal and the applicant has met with the bioavailability requirements. However, the sponsor has calculated the dose administered to the patients in the study 192371-002 based on a drop volume of 28.5 µl, but the label indicates a drop size of ——. With very low concentrations with the 0.05% cyclosporin, this increase in drop volume will not be show any significant and meaningful increase the blood levels.

/S/ 5/24/99

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Peer Reviewer: E. Dennis Bashaw, Pharm. D. /S/

CC: NDA 21-023 (ORIG)
HFD-550/Div File
HFD-550/CSO/Gorski
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-870(attn:CDR.B.Murphy)
HFD-344(Viswanathan)

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APPENDIX

NDA 21-023

Table IV. Trough blood cyclosporin A concentrations at weeks 1, 4 and 12 in dry eye human subjects treated twice daily in each eye with 0.05% cyclosporine emulsion for 12 weeks.

0.05% Cyclosporine Group

Trough Blood Cyclosporin A Concentration (ng/ml)			
Patient	Week 1	Week 4	Week 12
A05	<0.1	<0.1	<0.1
A10	<0.1	<0.1	<0.1
A13	<0.1	<0.1	<0.1
A16	<0.1	<0.1	<0.1
B04	<0.1	<0.1	<0.1
B10	<0.1	<0.1	<0.1
B11	<0.1	<0.1	<0.1
B19	<0.1	<0.1	<0.1
C04	<0.1	<0.1	<0.1
C08	<0.1	<0.1	<0.1
C12	<0.1	<0.1	<0.1
D01	<0.1	<0.1	<0.1
D08	<0.1	<0.1	<0.1
D16	<0.1	<0.1	<0.1
E02	<0.1	<0.1	<0.1
E08	<0.1	<0.1	<0.1
F05	<0.1	<0.1	<0.1
F06	<0.1	<0.1	<0.1
F13	<0.1	<0.1	<0.1
F18	<0.1	<0.1	<0.1
G02	<0.1	<0.1	<0.1
G13	<0.1	<0.1	<0.1
H05	<0.1	<0.1	<0.1
H07	<0.1	<0.1	<0.1
H15	<0.1	NA	<0.1
H17	<0.1	<0.1	<0.1
J04	<0.1	NA	NA
J06	<0.1	<0.1	<0.1
K04	<0.1	<0.1	<0.1
K08	<0.1	<0.1	<0.1
K11	<0.1	<0.1	<0.1
N	31	29	30
Range (ng/ml)	<0.1	<0.1	<0.1

NA is sample not available
BLQ (below limit of quantitation) values are replaced by <0.1 ng/ml for 0.05%-0.4% groups
Reference: L-1996-3953; L-1996-3954; L-1996-3955; L-1996-4352; L-1996-4300

Table V. Trough blood cyclosporin A concentrations at weeks 1, 4 and 12 in dry eye human subjects treated twice daily in each eye with 0.1% cyclosporine emulsion for 12 weeks.

0.1% Cyclosporine Group

Trough Blood Cyclosporin A Concentration (ng/ml)			
Patient No.	Week 1	Week 4	Week 12
A02	<0.1	<0.1	<0.1
A07	<0.1	<0.1	<0.1
A12	<0.1	<0.1	<0.1
A17	<0.1	<0.1	<0.1
B03	<0.1	<0.1	<0.1
B07	<0.1	<0.1	<0.1
B12	<0.1	<0.1	<0.1
B16	<0.1	<0.1	<0.1
C05	<0.1	<0.1	<0.1
C10	<0.1	<0.1	<0.1
C13	<0.1	<0.1	<0.1
D05	<0.1	<0.1	<0.1
D06	——	<0.1	<0.1
D18	<0.1	<0.1	<0.1
E04	<0.1	<0.1	<0.1
E07	<0.1	<0.1	<0.1
E12	<0.1	<0.1	<0.1
F02	<0.1	<0.1	<0.1
F07	<0.1	<0.1	<0.1
F14	<0.1	<0.1	<0.1
F17	<0.1	<0.1	<0.1
G04	<0.1	<0.1	<0.1
H02	<0.1	<0.1	<0.1
H10	<0.1	<0.1	<0.1
H14	<0.1	<0.1	<0.1
H16	<0.1	<0.1	<0.1
J03	<0.1	<0.1	<0.1
J08	<0.1	<0.1	<0.1
K03	<0.1	<0.1	<0.1
K09	<0.1	<0.1	NA
K14	<0.1	<0.1	<0.1
K17	<0.1	<0.1	NA
N	32	32	30
Range (ng/ml)	<0.1 to ——	<0.1	<0.1

NA is sample not available
BLQ (below limit of quantitation) values are replaced by < 0.1 ng/ml for 0.05%-0.4% groups
Reference: L-1996-3953; L-1996-3954; L-1996-3955; L-1996-4352; L-1996-4300

Table VI. Trough blood cyclosporin A concentration at weeks 1, 4 and 12 in dry eye hum subjects treated twice daily in each eye with 0.2% cyclosporine emulsion for 12 weeks.

0.2% Cyclosporine Group

Trough Blood Cyclosporin A Concentration (ng/ml)			
Patient No.	Week 1	Week 4	Week 12
A04	< 0.1	< 0.1	< 0.1
A06	< 0.1	< 0.1	< 0.1
A11	< 0.1	—	< 0.1
A18	< 0.1	< 0.1	< 0.1
B02	< 0.1	< 0.1	< 0.1
B06	< 0.1	< 0.1	< 0.1
B13	< 0.1	< 0.1	< 0.1
B17	< 0.1	< 0.1	< 0.1
C03	< 0.1	< 0.1	< 0.1
C09	< 0.1	< 0.1	< 0.1
C11	< 0.1	< 0.1	< 0.1
D02	< 0.1	< 0.1	< 0.1
D10	< 0.1	< 0.1	< 0.1
D12	< 0.1	< 0.1	< 0.1
D17	< 0.1	< 0.1	< 0.1
E03	< 0.1	< 0.1	—
E10	< 0.1	< 0.1	< 0.1
E13	< 0.1	< 0.1	< 0.1
F03	< 0.1	< 0.1	< 0.1
F10	< 0.1	< 0.1	< 0.1
F11	< 0.1	< 0.1	< 0.1
F20	< 0.1	< 0.1	< 0.1
G01	< 0.1	< 0.1	< 0.1
G11	< 0.1	< 0.1	< 0.1
H03	< 0.1	NA	NA
H12	< 0.1	< 0.1	< 0.1
H19	< 0.1	< 0.1	< 0.1
J05	< 0.1	< 0.1	< 0.1
J07	< 0.1	< 0.1	< 0.1
K01	< 0.1	< 0.1	< 0.1
K10	< 0.1	< 0.1	< 0.1
K15	< 0.1	< 0.1	< 0.1
K18	< 0.1	< 0.1	< 0.1
N	33	32	32
Range (ng/ml)	< 0.1	< 0.1 to —	< 0.1 to —

BLQ (below limit of quantitation) values are replaced by < 0.1 ng/ml for 0.05%-0.4% groups
NA is sample not available. L-1996-3953; L-1996-3954; L-1996-3955; L-1996-4352; L-1996-4300

Table VII. Trough blood cyclosporin A concentration at weeks 1, 4 and 12 in dry eye human subjects treated twice daily in each eye with 0.4% cyclosporine emulsion for 12 weeks.

0.4% Cyclosporine

Trough Blood Cyclosporin A Concentration (ng/ml)			
Patient No.	Week 1	Week 4	Week 12
A03	< 0.1	—	< 0.1
A09	< 0.1	—	< 0.1
A14	< 0.1	< 0.1	< 0.1
A19	< 0.1	< 0.1	< 0.1
B05	< 0.1	< 0.1	< 0.1
B08	< 0.1	< 0.1	< 0.1
B14	< 0.1	< 0.1	< 0.1
B18	< 0.1	< 0.1	< 0.1
C02	< 0.1	< 0.1	< 0.1
C06	< 0.1	< 0.1	< 0.1
C14	< 0.1	< 0.1	< 0.1
D09	< 0.1	< 0.1	< 0.1
D13	< 0.1	< 0.1	< 0.1
D20	< 0.1	< 0.1	< 0.1
E01	< 0.1	< 0.1	< 0.1
E09	< 0.1	< 0.1	< 0.1
E11	< 0.1	< 0.1	< 0.1
F04	< 0.1	< 0.1	< 0.1
F09	< 0.1	< 0.1	< 0.1
F15	< 0.1	< 0.1	< 0.1
F19	< 0.1	< 0.1	< 0.1
G05	< 0.1	< 0.1	< 0.1
G14	< 0.1	< 0.1	< 0.1
H04	< 0.1	< 0.1	NA
H09	< 0.1	< 0.1	< 0.1
H13	< 0.1	< 0.1	< 0.1
J01	< 0.1	< 0.1	< 0.1
K02	< 0.1	< 0.1	< 0.1
K06	< 0.1	< 0.1	NA
K13	< 0.1	< 0.1	< 0.1
N	30	30	28
Range (ng/ml)	< 0.1	< 0.1 to —	< 0.1

NA is sample not available
BLQ (below limit of quantitation) values are replaced by < 0.1 ng/ml for 0.05%-0.4% groups
Reference: L-1996-3953; L-1996-3954; L-1996-3955 L-1996-4352; L-1996-4300

Table VIII. Cyclosporin A concentrations (ng/ml) in blood samples collected at 1, 2 and 4 hours after the last dose of 0.05%, 0.1%, 0.2% or 0.4% cyclosporine emulsion was instilled in each eye of dry eye human subjects treated topically for 12 weeks.

Blood Cyclosporin A Concentrations (ng/ml) at 1-4 h in Week 12

0.05% Cyclosporine Group

Time (hours)	Patient A05	Patient A10	Patient A13	Patient A16	Patient G13
1	<0.1	<0.1	<0.1	<0.1	<0.1
2	<0.1	<0.1	<0.1	<0.1	<0.1
4	<0.1	<0.1	<0.1	<0.1	<0.1
N	3	3	3	3	3
Range (ng/ml)	<0.1	<0.1	<0.1	<0.1	<0.1

0.1% Cyclosporine Group

Time (hours)	Patient A07	Patient A12	Patient A17
1	<0.1	NA	<0.1
2	NA	<0.1	<0.1
4	<0.1	<0.1	<0.1
N	3	3	3
Range (ng/ml)	<0.1	<0.1	<0.1

0.2% Cyclosporine Group

Time (hours)	Patient A04	Patient A06	Patient G11
1	—	—	<0.1
2	—	<0.1	<0.1
4	—	<0.1	<0.1
N	3	3	3
Range (ng/ml)	— to —	<0.1 to —	<0.1

0.4% Cyclosporine Group

Time (hours)	Patient A09	Patient A14	Patient A19	Patient G14
1	<0.1	<0.1	—	<0.1
2	<0.1	<0.1	—	<0.1
4	<0.1	<0.1	<0.1	<0.1
N	3	3	3	3
Range (ng/ml)	<0.1	<0.1	<0.1 to —	<0.1

N is the total number of blood samples for each subject
NA means sample not available
BLQ (below limit of quantitation) values are replaced by < 0.1 ng/ml for 0.05%-0.4% groups
Reference: L-1996-3953; L-1996-3954; L-1996-3955; L-1996-4352; L-1996-4300

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ON ORIGINAL

Study 192371-002 (Report PK 98-109)

Formulations used in the study:

- Cyclosporine 0.05% ophthalmic emulsion (9054X, lot #11143)
- Cyclosporine 0.1% ophthalmic emulsion (8735X, lot #11101)
- Vehicle of cyclosporine ophthalmic emulsion (8922X, lot #11102)

Formulations were packaged in unit dose containers that dispensed a mean drop volume of 28.5 µL

Table IV. **Trough blood cyclosporin A concentrations at all 3 sampling times in patients who possessed at least 1 quantifiable blood concentration after 1 or 6 months of topical administration of 0.05% or 0.1% cyclosporine ophthalmic emulsions to both eyes twice-daily.**

Patient	Age, sex	Blood cyclosporin A concentration (ng/mL)		
		Day 0 (prestudy)	Month 1	Month 6
198	86, female	BLQ	BLQ	—
203	81, female	BLQ	BLQ	—
206	52, female	BLQ	BLQ	—
213	56, male	BLQ	—	BLQ
402	56, female	BLQ	—	NS[a]
410	64, female	BLQ	—	BLQ

[a] no sample was collected from this patient at Month 6

Table V. **Highest individual trough blood cyclosporin A concentrations measured after 1 and 6 months of topical administration of vehicle, 0.05% or 0.1% cyclosporine ophthalmic emulsions to both eyes twice-daily.**

Cyclosporine treatment group	Blood cyclosporin A concentration (ng/mL):		
	Day 0 (prestudy)	Month 1	Month 6
Vehicle	<0.1	<0.1	<0.1
0.05%	<0.1	<0.1	<0.1
0.1%	<0.1	—	—

[a] the highest of 3 quantifiable blood concentrations that were collected at Month 1.

[b] the highest of 3 quantifiable blood concentrations that were collected at Month 6.

Table III. **Cyclosporin A concentrations in all blood samples containing a quantifiable concentration of cyclosporin A.**

Patient	Cyclosporine emulsion	C_{max} (ng/mL)	t_{max} (hr)
242	0.1%[a]	—	2
239	0.1% (vehicle)[b]	—	1
245	0.1% (vehicle)[b]	—	3

[a] was treated with 0.1% cyclosporine emulsion since start of study

[b] was originally in vehicle treatment group, but was switched to 0.1% cyclosporine emulsion at month 6