

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-369**

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-369
Original

NDA 20-369
Amendment

Submission date: 7/28/93 11/5/93
Received date: 7/29/93 11/8/93
Review date: 2/16/94

Sponsor:

Alcon Laboratories
6201 South Freeway
Fort Worth, TX 76101
(817) 293-0450

Drug:

CILOXAN

Generic:

Ciprofloxacin HCl Ophthalmic Ointment

Chemical:

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid.

Pharmacologic Category:

Ciprofloxacin HCl is a fluoroquinolone antimicrobial.

Proposed Indication:

For the treatment of infections caused by susceptible strains of the designated microorganisms in conjunctivitis and corneal ulcers.

Proposed Dosage Form and Route of Administration:

Topical, Ophthalmic Ointment

Proposed Dosing:

The recommended dosage regimen for the treatment of **corneal ulcers** is: apply a 1/2" ribbon into the conjunctival sac (between the eyeball and the lower lid) every 1-2 hours around the clock on the first two days, then apply a 1/2" ribbon every 4 hours for up to 12 days. Dosing may be extended at the discretion and instructions of the prescribing physician.

The recommended dosage regimen for the treatment of **conjunctivitis**: apply a 1/2" ribbon into the conjunctival sac three times a day on the first two days, then apply a 1/2" ribbon two times a day for the next five days. Dosing may be extended at the discretion and instructions of the prescribing physician.

Related
Submissions:

NDA 19-992 (Ciloxan Solution)

Scientific Rationale

Review Comments:

The sponsor has submitted the same rationale for this new dosage form that was submitted for the approved ciprofloxacin ophthalmic solution. The rationale for the ointment form, short of to be used in children, is not clear. Perhaps the best idea of the sponsor's intention for the use of this drug is grasped when you read page 2-15 of the submission, the following paragraph;

" Ciprofloxacin Ophthalmic Ointment 0.3% could be used as adjunctive therapy with the solution, i.e. for treatment at bedtime. The availability of the ointment would offer physicians a choice of dosage forms in treating bacterial infections of the eye, allowing for greater utility of an excellent topical antibacterial agent."

Reviewer's Comments: *Having already an approved ophthalmic solution for the same indication, this dosage form in the opinion of this reviewer is impractical especially for the adult population due to the inherent properties of the ointment formulation. The mere mentioning of "adjunctive therapy" is disturbing. Is the sponsor implying that the approved solution needs adjunctive therapy? In any case, no adjunctive therapy studies were performed and it should be made very clear that this is intended as a substitution therapy. To put this very simple "patients should not be prescribed a vial of the solution and a tube of the ointment when it is not necessary".*

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ON ORIGINAL**

Conjunctivitis

Protocol No.	Study Patients and Objectives	Medications	Number Patients	
			Safety	Efficacy
C-88-24	Conjunctivitis - Compare Ciprofloxacin to TOBREX	Ciprofloxacin, 0.3% TOBREX	244 253	87 91
C-88-94	Conjunctivitis - Compare Ciprofloxacin to Placebo	Ciprofloxacin 0.3% Placebo	70 74	29 42

Corneal Ulcers

Protocol No.	Study Patients and Objectives	Medications	Number Patients	
			Safety	Efficacy
C-90-85 Study 1	Bacterial Corneal Ulcers - Safety/Efficacy Evaluation	Ciprofloxacin 0.3% Open-Label	166	106
C-90-85 Study 2	Bacterial Corneal Ulcers - Safety/Efficacy Evaluation	Ciprofloxacin 0.3% Open-Label	87	39

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Study #1**Ciprofloxacin vs Placebo (C-88-94)**

This study is a randomized, controlled and double-masked comparison of the efficacy and safety of Ciprofloxacin Ophthalmic Ointment 0.3% and Placebo (Vehicle). Ten investigators at seven cities participated in this multiclinic evaluation. A total of 144 patients with clinically diagnosed bacterial conjunctivitis were enrolled in this study. Of these, all 144 patients were evaluative for safety and 71 conjunctivitis patients were evaluative for efficacy.

If the patient was eligible for the study based on inclusion and exclusion criteria, the study details were explained and a signed and witnessed informed consent was obtained. A history of each patient was obtained, an ocular exam performed, and ocular signs and symptoms were recorded. An entrance pregnancy test was administered to female patients if they were not prepubertal, postmenopausal, had a hysterectomy or a bilateral oophorectomy.

Bacterial specimens were obtained from the conjunctiva of each affected eye of each enrolled patient according to the regimen described in the protocol. Conjunctival specimens were designated as either culture-positive or culture-negative for bacteria based on threshold levels defined in the protocol. The threshold criteria for culture-positive specimens were as follows:

Group I - Threshold = 1 CFU/mL (i.e., any counts)

Streptococcus, Group A, β hemolytic (*S. pyogenes*)
Streptococcus pneumoniae
Citrobacter
Enterobacter
Escherichia
Klebsiella
Proteus/Morganella
Serratia marcescens
Other Enterobacteriaceae
Neisseria gonorrhoeae
Other Neisseria
Other Moraxella
Acinetobacter
Achromobacter
Haemophilus
Pseudomonas aeruginosa
Other *Pseudomonas*

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Group II - Threshold = 10 CFU/mL

Staphylococcus aureus
Streptococcus Group B (β or nonhemolytic)
Streptococcus Group C (α , β or nonhemolytic)
Other *Streptococcus* (Groups D, G; nongrouped; viridans)
Moraxella (Branhamella) catarrhalis

Group III - Threshold = 100 CFU/mL

Staphylococcus epidermidis
Other coagulase-negative *staphylococcus*
Micrococcus
Bacillus

Group IV - Threshold = 1000 CFU/mL

Corynebacterium (diphtheroids)

Note: An ocular specimen was considered "Culture Positive" if colony count equaled or exceeded the threshold values given for any of the groups of organisms listed.

The masked medication (ciprofloxacin or placebo) was issued to the patient according to a computerized random treatment code. The investigator demonstrated to the patient the procedure for instilling the drug. The patient was instructed to instill a 1/2" ribbon three times a day into each affected eye on Days 0 and 1 and a 1/2" ribbon two times a day on Day 2. In addition, the patient received an instruction sheet containing the dosing information. Dosing was discontinued at 10 p.m. on the night before the third required visit with exam and culture (Day 3).

Clinical observation and evaluation of signs and symptoms were performed on Days 0, 1, 2 and 3. The conjunctiva(e) of the affected eye(s) were cultured for bacteria on Days 0 and 3. Signs and symptoms were evaluated and recorded at each visit, as well as physician judgment.

Discontinuation of treatment occurred for any of the following reasons: worsening of the disease (two or more signs or symptoms significantly worsened); clinically significant adverse medical event; protocol violation; personal reasons.

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The efficacy of Ciprofloxacin Ophthalmic Ointment 0.3% relative to placebo was determined by evaluating three parameters: the bacteriological counts of the conjunctival specimens at Day 3 relative to Day 0, the physician's clinical judgment at Day 3 regarding overall resolution of disease and severity scores assigned to five cardinal clinical signs of conjunctivitis. The cardinal signs evaluated were: erythema, exudation, discharge, and palpebral and bulbar conjunctival inflammation. Therefore, bacterial culture results, physician follow-up judgment and resolution of the cardinal ocular signs were the major efficacy variables analyzed statistically.

Microbiological efficacy was analyzed statistically by comparing the eradication rates of the bacterial cultures obtained on Day 3 relative to those obtained on Day 0. The counts or quantified numbers of microorganisms was classified as "eradicated", "reduced", "persistent", or "proliferated" relative to the Day 0 culture. These terms are defined as follows:

Verdict	Definition
Eradication (E)	Infection Organism originally present above threshold on Day 0 is absent in follow-up culture.
Reduction (R)	Pathogen originally present above threshold on Day 0 is reduced to a count below threshold in a follow-up culture.
Persistence (NC)	Pathogen originally present above threshold on Day 0 is reduced to a count below Day 0 count, but is above or equal to threshold in follow-up culture.
Proliferation (P)	Pathogen originally present above threshold on Day 0 is increased to a count above Day 0 count in follow-up culture.

Bacteriological success was achieved if the offending microorganism isolated on Day 0 was eradicated or reduced below the relative organism threshold level on Day 3.

To statistically compare the microbiological efficacy of ciprofloxacin and placebo, microbiological efficacy scores were assigned on a per patient basis (0 = eradicated, 1 = reduced, 2 = persisted and 3 = proliferated). For unilateral culture-positive patients, microbiological results for the infected eye were used. For bilateral culture-positive patients, microbiological efficacy for the "worse eye" was assigned based on the eye that had the least desirable microbiological response to treatment (proliferation = least desirable, eradication = most desirable). Microbiological efficacy scores and microbiological success were statistically analyzed using the Cochran-Mantel-Haenszel Rank Score test.

Clinical observations were made by the investigator on Days 1, 2, and 3 by evaluating the patient's overall clinical condition. The investigator made one of the following judgments regarding the patient's response to therapy at each follow-up visit: Cured (score 0) = absence of signs or symptoms; Better (score 1) = a unit change in two or more signs or symptoms; Unchanged (score 2) = no response in overall change in signs or symptoms;

Worse (score 3) = overall increase in signs or symptoms. The scores assigned to the physician's evaluations were statistically evaluated using the Cochran-Mantel-Haenszel Rank Score test.

The scoring of ocular signs and symptoms (minimum, zero - not present; maximum, three - severe) was reflective of the conjunctivitis, not of the transient symptomatology related to instillation of medication. At Days 0, 1, 2, and 3 the investigator assigned the following severity scores to each of the signs and symptoms evaluated: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Scoring standardization was obtained by referring to a manual of definitions which was contained in the Case Report Form. The following ocular symptoms were evaluated: discomfort, acute ocular pain, tearing, photophobia and itching. The ocular signs that were evaluated included: erythema, discharge, exudation, bulbar and palpebral conjunctival inflammation, limbal changes, epithelial disease, focal stromal infiltration, and aqueous reaction (cells and flare).

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Flow Chart

Activity	Day 0 Visit	Day 1 Visit	Day 2 Visit	Day 3 Visit
Patient Screening	X			
Informed Consent Obtained	X			
Patient History Taken	X			
Pregnancy Test Administered, If Applicable	X			X
Visual Acuity Taken	X	X	X	X
Ocular Signs and Symptoms Obtained	X	X	X	X
Bacterial Specimens Collected	X			X ^a
Instillation of Medication Initiated	X			
Physician's Follow-up Judgment Made		X	X	X
Instillation of Medication Terminated			X ^b	
Exit Form Completed				X
Medical Event Form Completed, If Applicable		X	X	X

^aFinal microbiological specimen obtained at least 6 hours after the final instillation of study drug.

^bStudy drug was dosed for 3 (\pm 1) days.

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LIST OF INVESTIGATORS

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
1182	Richard E. Bensinger, M.D. 1221 Madison Street, Room 1220 Seattle, WA 98104	10/18/90 - 08/17/92
1148	Jeffrey M. Couch, M.D. 2700 Hospital Drive North Kansas City, MO 64116	02/06/90 - 09/06/90
552	Warren R. Fagadau, M.D. 6131 Luther Lane #216 Dallas, TX 75225	04/12/90 - 08/17/92
943*	Robert A. Laibovitz, M.D. 3307 Northland Dr. - Suite 470 Austin, TX 78731	11/03/89 - 09/07/90 09/26/91 - 08/17/92
498	James P. McCulley, M.D. UTHSC - Dallas 5323 Harry Hines Blvd. Dallas, TX 75235	01/30/90 - 08/17/92
1523	Marc A. Mintz, D.O. 11627 E. Telegraph Rd. Santa Fe Springs, CA 90670	05/08/92 - 08/17/92
1214	Richard G. Orlando, M.D. Future Healthcare Research Center 3100 Olentangy Road Columbus, OH 43202	10/19/90 - 04/13/92
1027	Rex L. Repass, M.D. 4029 S. Capital of Texas Highway Suite 212 Austin, TX 78704	10/03/91 - 01/20/92

* Investigator in study C-88-24

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LIST OF INVESTIGATORS - Continued

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
271	Robert H. Stewart, M.D. Houston Eye Associates 2855 Gramercy Houston, TX 77025	05/14/90 - 09/07/90
1007	Thomas R. Walters, M.D. 4029 S. Capital of Texas Highway Suite 212 Austin, TX 78704	02/4/92 - 08/17/92

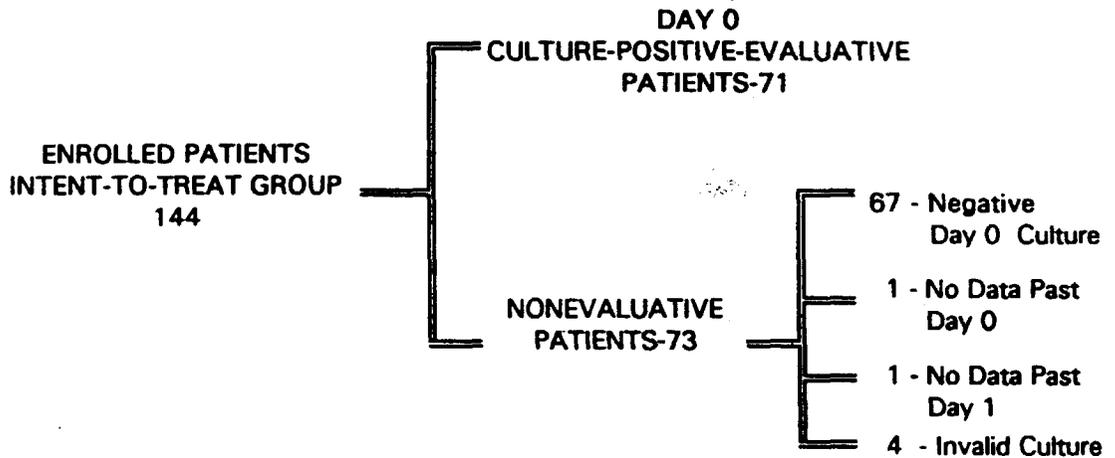
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Patient Enrollment - Evaluation By Protocol

Conjunctivitis

Protocol No.	Study Patients and Objectives	Medications	Number Patients	
			Safety	Efficacy
C-88-94	Conjunctivitis - Compare Ciprofloxacin to Placebo	Ciprofloxacin 0.3% Placebo	70	29
			74	42

A total of 144 patients with clinically diagnosed bacterial conjunctivitis were enrolled in this study. Of these, all 144 patients were evaluative for safety and 71 conjunctivitis patients were evaluative for efficacy. Patients were considered to be evaluative for safety if they had instilled the medication at least once. Patients were considered to be evaluative for efficacy if they were conjunctival culture-positive on Day 0, dosed with medication for at least three days and returned for their Day 3 follow-up exam and culture. The distribution of all patients enrolled in this study are presented in Figure 4 as follows:



Ciprofloxacin Versus Placebo Study (C-88-94)

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Demographics**Culture Positive-Evaluative Group**

Age					
	N	Mean	STD	MIN	MAX
Ciprofloxacin	29	34.2	25.71	2.0	85.0
Placebo	42	27.8	24.59	1.0	88.0

$p = 0.29$, Two-sample t-test

		Sex			
		Male		Female	
	TOTAL	N	%	N	%
Ciprofloxacin	29	16	55.2	13	44.8
Placebo	42	19	45.2	23	54.8

$p = 0.41$, Chi-square test for independence

		Race					
		White		Black		Hisp.	
	TOTAL	N	%	N	%	N	%
Ciprofloxacin	29	18	62.1	4	13.8	7	24.1
Placebo	42	21	50.0	6	14.3	15	35.7

$p = 0.28$, Chi-square test for independence

Duration (DAYS)					
	N	Mean	STD	MIN	MAX
Ciprofloxacin	29	4.8	5.33		
Placebo	42	6.4	10.35		

$p = 0.42$, Two-sample t-test

Reviewer's Comments: *No significant treatment differences were found for any of the demographic characteristics of the culture-positive patients.*

Intent - to - Treat Group

Age				
	N	Mean	STD	RANGE
Ciprofloxacin	70	29.5	22.37	2 - 85
Placebo	74	28.1	22.14	1 - 88

p = 0.72, Two-sample t-test

	TOTAL	Sex			
		Male		Female	
		N	%	N	%
Ciprofloxacin	70	30	42.9	40	57.1
Placebo	74	35	47.3	39	52.7

p = 0.59, Chi-square test for independence

	TOTAL	Race							
		White		Black		Hisp.		Other	
		N	%	N	%	N	%	N	%
Ciprofloxacin	70	38	54.3	12	17.1	19	27.1	1	1.5
Placebo	74	44	59.5	11	14.9	19	25.7	-	-

p = 0.60, Chi-square test for independence

Duration				
	N	Mean	STD	RANGE
Ciprofloxacin	70	4.2	4.84	
Placebo	74	5.9	9.12	

p = 0.16, Two-sample t-test

Reviewer's Comments: *No significant treatment differences were observed for the intent-to-treat group with respect to age, sex or race.*

Patient Enrollment by Investigator and by Study
 Protocol C-88-94
 (Ciprofloxacin vs Placebo)

Investigators		Patient Distribution Ciprofloxacin/Placebo		
Number	Name	Enrolled	Evaluative for Safety	Evaluative for Efficacy
1182	Bensingher	5	5	5
1148	Couch	11	11	6
552	Fagadau	7	7	4
943	Laibovitz	26	26	17
498	McCulley	25	25	12
1523	Mintz	40	40	24
1214	Orlando	11	11	0
1027	Repass	5	5	0
271	Stewart	12	12	3
1007	Walters	2	2	0
Totals	10	144	144¹	71²

¹Evaluated in the intent-to-treat group.

²Evaluated in the culture-positive evaluative group.

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Distribution of Day 0 Conjunctival Infective Organisms
in Patients Evaluative For Efficacy

Organism	Ciprofloxacin	Placebo	Total
<u>Gram-Positive:</u>			
<i>Staphylococcus epidermidis</i>	5	12	17
<i>Staphylococcus aureus</i>	0	24	34
<i>Staphylococcus</i> , Coeg. - Neg., other	3	1	4
<i>Streptococcus, pneumoniae</i>	0	1	1
<i>Streptococcus</i> , Groups D,G, or Viridans	4	10	14
<i>Corynebacterium</i> spp. (diphtheroids)	2	2	4
<i>Micrococcus</i> spp.	1	1	2
Subtotal	25	51	76
<u>Gram-Negative:</u>			
<i>Haemophilus influenzae</i> (incl. <i>H. aegyptius</i>)	6	5	11
<i>Acinetobacter</i> spp.	4	2	6
<i>Neisseria</i> spp.	2	1	3
<i>Pseudomonas</i> spp. (not <i>P. aeruginosa</i>)	2	0	2
<i>Proteus/Morganella</i> spp.	2	1	3
<i>Klebsiella</i> spp.	0	1	1
<i>Escherichia coli</i>	1	0	1
<i>Enterobacter</i> spp.	4	0	4
<i>Enterobacteriaceae</i> , other	1	0	1
Subtotal	22	10	32
Grand Total	47	61	108

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Microbiology ResultsEvaluative Patients-Microbiological and Clinical Results
Protocol C-88-94Treated with Ciprofloxacin

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0271	2010	<i>Haemophilus sp.</i>	Eradication	Better
0498	5003	<i>Staphylococcus aureus</i>	Proliferation	Unchanged
	5004	<i>Staphylococcus epidermidis</i>	Eradication	Unchanged
	5008	<i>Other Streptococcus Escherichia coli</i>	Persistence	Better
	5019	<i>Haemophilus influenzae</i>	Eradication	Cured
	5024	<i>Enterobacteriaceae sp.</i>	Eradication	Better
0552	7002	<i>Staphylococcus epidermidis</i>	Proliferation	Unchanged
	7007	<i>Staphylococcus sp.</i>	Reduction	Unchanged
0943	4003	<i>Acinetobacter sp.</i>	Eradication	Better
	4005	<i>Pseudomonas sp.</i>	Eradication	Better
	4007	<i>Staphylococcus epidermidis</i> <i>Pseudomonas sp.</i>	Reduction	Cured
	4009	<i>Staphylococcus aureus</i>	Eradication	Better
	4015	<i>Staphylococcus aureus</i>	Eradication	Better
	4018	<i>Other coagulase negative Staphylococcus</i> <i>Acinetobacter sp.</i> <i>Enterobacter sp.</i>	Reduction	Better
	4019	<i>Micrococcus sp.</i> <i>Proteus/Morganella sp.</i>	Eradication	Better
	4022	<i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i>	Eradication	Cured

APPEARS THIS WAY
ON ORIGINAL

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
1148	6002	<i>Acinetobacter sp.</i>	Eradication	Cured
	6006	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	6011	<i>Streptococcus sp.</i> <i>Proteus/Morganella sp.</i>	Eradication	Cured
1182	1002	<i>Neisseria sp.</i> <i>Staphylococcus epidermidis</i> <i>Staphylococcus sp.</i> <i>Streptococcus sp.</i>	Eradication	Better
	1003	<i>Streptococcus sp.</i> <i>Neisseria sp.</i>	Eradication	Better
1523	1503	<i>Enterobacter sp.</i>	Eradication	Cured
	1504	<i>Staphylococcus aureus</i> <i>Haemophilus influenzae</i>	Proliferation	Cured
	1507	<i>Enterobacter sp.</i>	Proliferation	Cured
	1523	<i>Staphylococcus aureus</i>	Eradication	Cured
	1526	<i>Staphylococcus aureus</i> <i>Haemophilus influenzae</i>	Eradication	Cured
	1527	<i>Staphylococcus aureus</i>	Eradication	Cured
	1530	<i>Staphylococcus aureus</i>	Eradication	Cured
	1535	<i>Staphylococcus aureus</i> <i>Haemophilus influenzae</i>	Eradication	Cured

APPEARS THIS WAY
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B. Treated with Placebo

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0271	2008	<i>Proteus/Morganella sp.</i>	Eradication	Better
	2011	<i>Staphylococcus aureus</i>	Proliferation	Unchanged
0498	5001	<i>Staphylococcus aureus</i>	Proliferation	Unchanged
	5002	<i>Staphylococcus aureus</i>	Proliferation	Unchanged
	5009	<i>Staphylococcus aureus</i>	Eradication	Worse
	5011	<i>Staphylococcus aureus</i>	Persistence	Unchanged
	5013	<i>Streptococcus sp.</i>	Eradication	Worse
	5015	<i>Staphylococcus epidermidis</i>	Eradication	Better
	5018	<i>Staphylococcus sp.</i>	Eradication	Better
0552	7004	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i>	Persistence	Worse
	7006	<i>Staphylococcus aureus</i>	Persistence	Unchanged
0943	4001	<i>Staphylococcus epidermidis</i>	Reduction	Better
	4006	<i>Staphylococcus epidermidis</i>	Reduction	Unchanged
	4008	<i>Staphylococcus epidermidis</i>	Persistence	Unchanged
	4010	<i>Staphylococcus aureus</i>	Proliferation	Unchanged
	4011	<i>Haemophilus sp.</i>	Eradication	Cured
	4013	<i>Staphylococcus aureus</i> <i>Haemophilus influenzae</i>	Proliferation	Worse
	4020	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	4021	<i>Streptococcus pneumoniae</i>	Proliferation	Worse
	4025	<i>Staphylococcus epidermidis</i>	Eradication	Cured

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Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
1148	6001	<i>Streptococcus sp.</i>	Eradication	Cured
	6004	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i> <i>Klebsiella sp.</i>	Proliferation	Better
	6007	<i>Staphylococcus epidermidis</i>	Reduction	Better
1182	1001	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i> <i>Haemophilus influenzae</i>	Eradication	Better
	1004	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i> <i>Corynebacterium sp.</i>	Proliferation	Better
	1005	<i>Micrococcus sp.</i> <i>Streptococcus sp.</i> <i>Neisseria sp.</i>	Eradication	Unchanged
1523	1502	<i>Haemophilus influenzae</i>	Eradication	Better
	1505	<i>Staphylococcus aureus</i>	Eradication	Cured
	1506	<i>Staphylococcus aureus</i>	Eradication	Cured
	1509	<i>Acinetobacter sp.</i>	Eradication	Cured
	1510	<i>Staphylococcus aureus</i> <i>Corynebacterium sp.</i>	Eradication	Cured
	1517	<i>Staphylococcus aureus</i>	Eradication	Cured
	1522	<i>Staphylococcus aureus</i>	Eradication	Cured
	1524	<i>Staphylococcus aureus</i>	Persistence	Cured
	1525	<i>Staphylococcus aureus</i> <i>Streptococcus sp.</i>	Persistence	Cured
1528	<i>Staphylococcus aureus</i>	Eradication	Cured	

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
1523 -	1529	<i>Staphylococcus aureus</i>	Proliferation	Cured
Cont'd	1531	<i>Staphylococcus aureus</i>	Proliferation	Cured
	1533	<i>Staphylococcus aureus</i>	Persistence	Cured
	1536	<i>Staphylococcus aureus</i>	Eradication	Better
	1537	<i>Staphylococcus aureus</i>	Persistence	Cured
	1539	<i>Staphylococcus aureus</i> <i>Haemophilus influenzae</i>	Eradication	Cured

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	TOTAL	ERADICATION		REDUCTION		PERSISTENCE		PROLIFERATION	
		N	%	N	%	N	%	N	%
Ciprofloxacin	29	20	69.0	4	13.8	1	3.4	4	13.8
Placebo	42	21	50.0	3	7.1	8	19.0	10	23.8

$p = 0.08$, Cochran-Mantel-Haenszel Rank Score Test

Reviewer's Comments: *No statistically significant treatment differences were found for the comparison of microbiological eradication scores in culture-positive patients ($p = 0.08$). However, for the combination of eradication and reduction categories, ciprofloxacin was significantly ($p = 0.04$) more effective than placebo. There is a lack of correlation between microbiological results and clinical outcome.*

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**Distribution of Day 0 Conjunctival Infective Organisms
in Patients Evaluative for Efficacy**

Organism	Ciprofloxacin	Placebo	Total*
Gram-Positive:			
<i>Staphylococcus aureus</i>	10	24	34
<i>Staphylococcus epidermidis</i>	5	12	17
<i>Staphylococcus, Coag. - Neg., other</i>	3	1	4
<i>Streptococcus pneumoniae</i>	0	1	1
<i>Streptococcus, Groups D,G, or Viridans</i>	4	10	14
<i>Corynebacterium spp. (diphtheroids)</i>	2	2	4
<i>Micrococcus spp.</i>	1	1	2
Subtotal	25	51	76
Gram-Negative:			
<i>Haemophilus influenzae (incl. H. aegyptius)</i>	6	5	11
<i>Acinetobacter spp.</i>	4	2	6
<i>Neisseria spp.</i>	2	1	3
<i>Pseudomonas spp. (not P. aeruginosa)</i>	2	0	2
<i>Proteus/Morganella spp.</i>	2	1	3
<i>Klebsiella spp.</i>	0	1	1
<i>Escherichia coli</i>	1	0	1
<i>Enterobacter spp.</i>	4	0	4
<i>Enterobacteriaceae, other</i>	1	0	1
Subtotal	22	10	32
Grand Total	47	61	108

*Number of strains of bacteria isolated from 71 evaluative patients.

CLINICAL RESULTS:**Culture-Positive-Evaluative Group**

	TOTAL	Cured		Better		Unchanged		Worse	
		N	%	N	%	N	%	N	%
Cipro	29	14	48.2	11	37.9	4	13.8	-	-
Placebo	42	18	42.8	10	23.8	9	21.4	5	11.9

$p = 0.34$, Cochran-Mantel-Haenszel Rank Score Test

Culture-Positive-Evaluative Group

	TOTAL	Cured Day 1		Cured Day 2		Cured Day 3		Better		Unchanged		Worse	
		N	%	N	%	N	%	N	%	N	%	N	%
Cipro	29	-	-	7	24.1	7	24.1	11	37.9	4	13.8	-	-
Placebo	42	2	4.8	9	21.4	7	16.7	10	23.8	9	21.4	5	11.9

$p = 0.34$, Cochran-Mantel-Haenszel Rank Score Test

Reviewer's Comments: No statistically significant treatment difference was found ($p = 0.34$) in the culture-positive group.

Intent-to-Treat Group

	TOTAL*	Cured Day 1		Cured Day 2		Cured Day 3		Better		Unchanged		Worse	
		N	%	N	%	N	%	N	%	N	%	N	%
Cipro	65	1	1.5	11	16.9	24	36.9	23	35.4	5	7.7	1	1.5
Placebo	69	2	2.9	10	14.5	15	21.7	23	33.3	10	14.5	9	13.0

*Data on 10 patients for this parameter were not obtained.

$p = 0.03$, Cochran-Mantel-Haenszel Rank Score Test

Reviewer's Comments: A significant difference ($p = 0.03$) favoring ciprofloxacin was detected in the intent-to-treat group.

One investigator (No. 1523) clinically rated each of his 24 evaluative patients as cured or better. However, the clinical results of 8/24 (33%) of these patients did not corroborate their microbiological results. Furthermore, of the 17 patients in this study whose physician judgments disagreed with their microbiological outcomes, 8 (47%) were contributed by this investigator. Analysis of physician judgment ratings, excluding investigator 1523 data, showed Ciprofloxacin ointment to be significantly ($p = 0.02$) more effective than placebo for physician judgment.

Antibacterial Treatment Efficacies by Organism - Day 3

Infecting Organisms	Ciprofloxacin					Placebo				
	(n)	E	R	NC	P	(n)	E	R	NC	P
Gram-Positive:										
<i>Staphylococcus aureus</i>	(10)	8	0	0	2	(24)	11	0	7	6
<i>Staphylococcus epidermidis</i>	(5)	2	2	0	1	(12)	5	3	2	2
<i>Staphylococcus, Coag. - Neg., other</i>	(3)	1	2	0	0	(1)	1	0	0	0
<i>Streptococcus pneumoniae</i>	(0)	0	0	0	0	(1)	0	0	0	1
<i>Streptococcus, Group D,G, Viridans</i>	(4)	3	0	1	0	(10)	8	0	1	1
<i>Corynebacterium spp. (diphtheroids)</i>	(2)	2	0	0	0	(2)	1	0	1	0
<i>Micrococcus spp.</i>	(1)	1	0	0	0	(1)	1	0	0	0
Subtotal	(25)	17	4	1	3	(51)	27	3	11	10
(%)		(68.0)	(16.0)	(4.0)	(12.0)		(52.9)	(5.9)	(21.6)	(19.6)

Continued . . .

Legend: n = Total number of isolates per patient (worse case verdict) for each treatment group
 E = Eradication
 R = Reduction
 NC = Persistence
 P = Proliferation

APPEARS THIS WAY
ON ORIGINAL

Continued

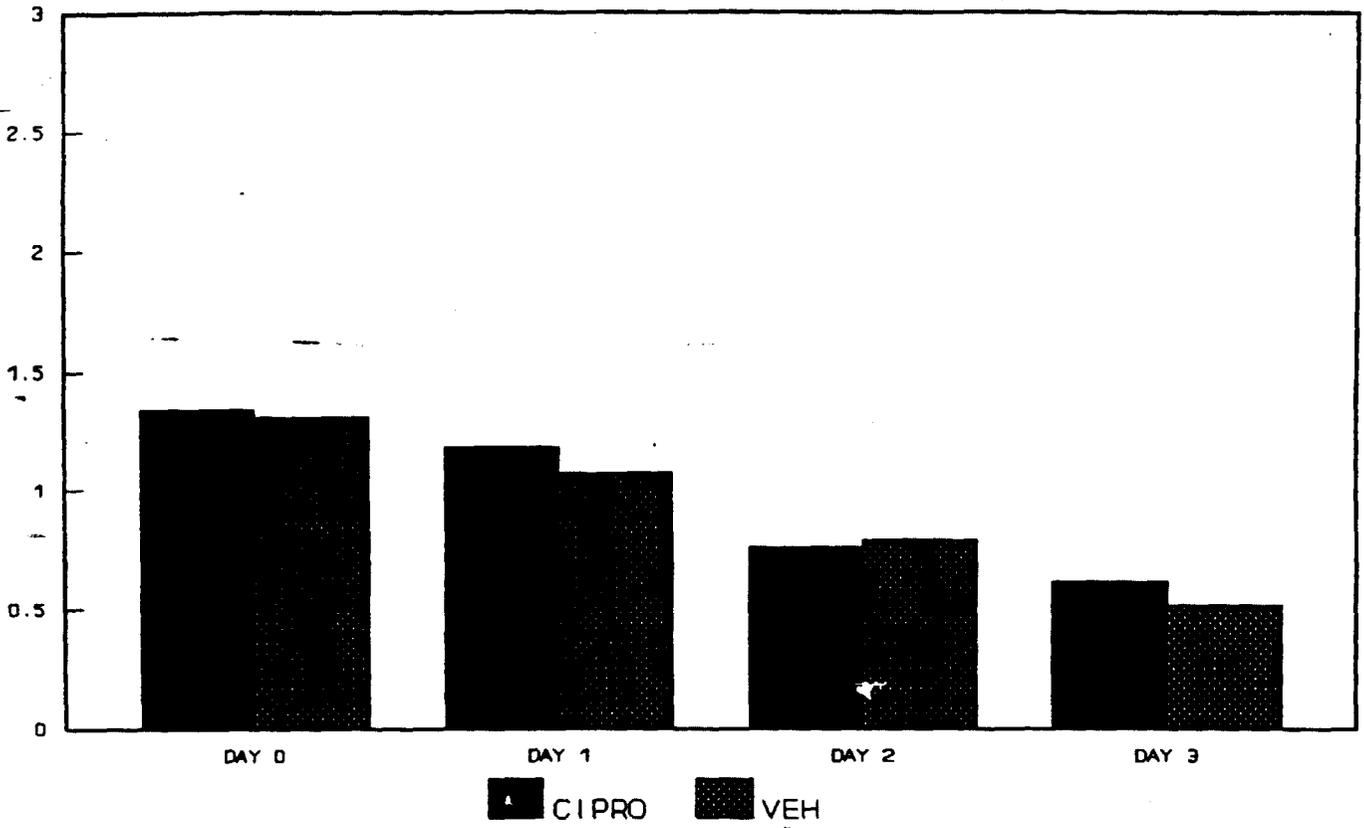
Infecting Organisms	Ciprofloxacin					Placebo				
	(n)	E	R	NC	P	(n)	E	R	NC	P
Gram-Negative:										
<i>Haemophilus influenzae</i> (incl. <i>H. aegyptius</i>)	(6)	5	0	0	1	(5)	5	0	0	0
<i>Acinetobacter spp.</i>	(4)	4	0	0	0	(2)	2	0	0	0
<i>Neisseria sp.</i>	(2)	(2)	0	0	0	(1)	1	0	0	0
<i>Pseudomonas spp. (not P. aeruginosa)</i>	(2)	2	0	0	0	0	0	0	0	0
<i>Enterobacter spp.</i>	(4)	3	0	0	1	(0)	0	0	0	0
<i>Klebsiella spp.</i>	(0)	0	0	0	0	(1)	1	0	0	0
<i>Escherchia coli</i>	(1)	(1)	0	0	0	(0)	0	0	0	0
<i>Proteus/Morganella spp.</i>	(2)	2	0	0	0	(1)	1	0	0	0
<i>Enterobacteriaceae, other</i>	(1)	1	0	0	0	(0)	0	0	0	0
Subtotal	(22)	20	0	0	2	(10)	10	0	0	0
(%)		(90.9)	(0)	(0)	(9.1)		(100.0)	(0)	(0)	(0)
Grand Total	(47)	37	4	1	5	(61)	37	3	11	10
(%)		(78.7)	(8.5)	(2.1)	(10.8)		(60.7)	(4.9)	(18.0)	(16.4)

APPEARS THIS WAY
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CLINICAL CARDINAL SIGNS MOST COMMONLY ASSOCIATED WITH BACTERIAL CONJUNCTIVITIS

ERYTHEMA

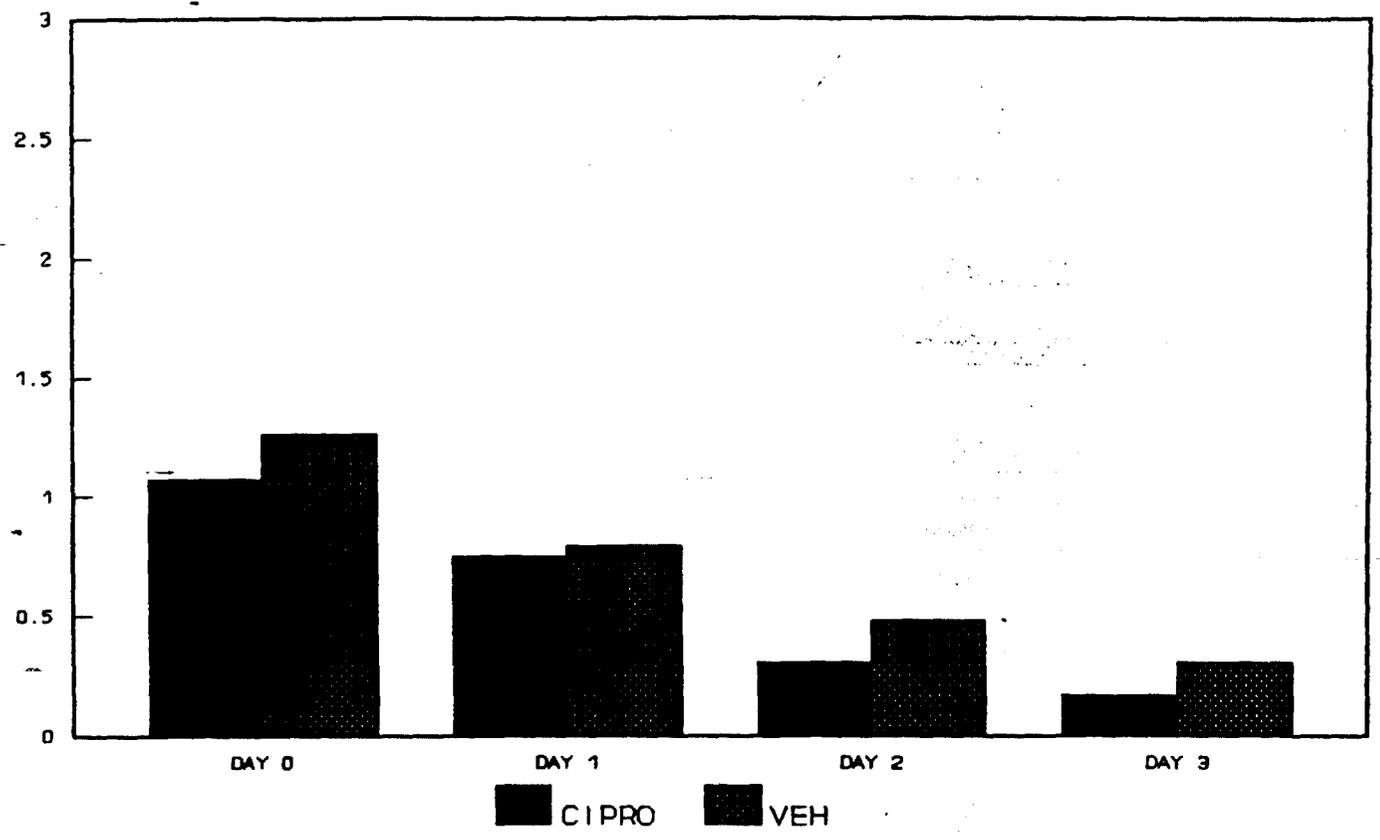
MEAN SCORES



APPEARS THIS WAY
ON ORIGINAL

DISCHARGE

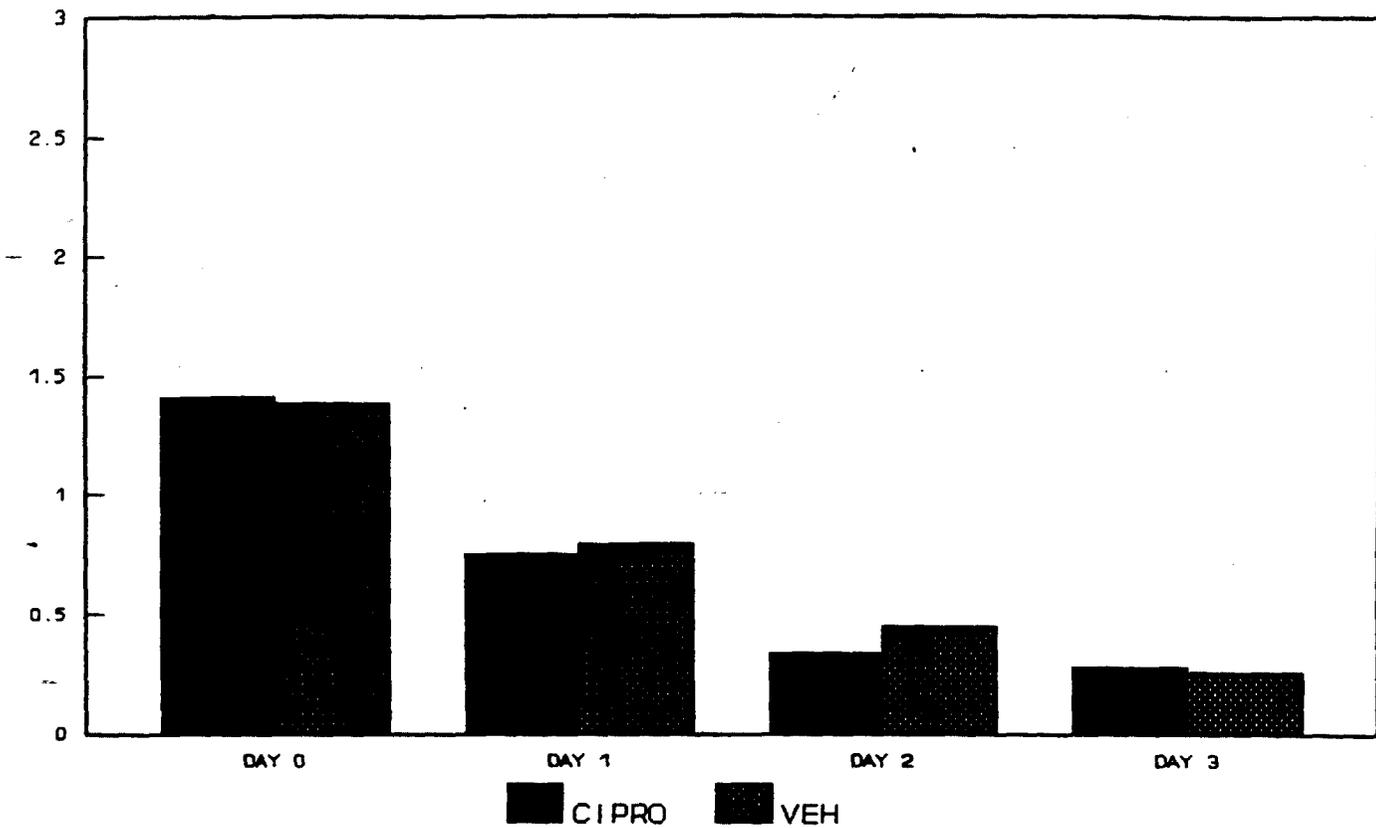
MEAN SCORES



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ON ORIGINAL

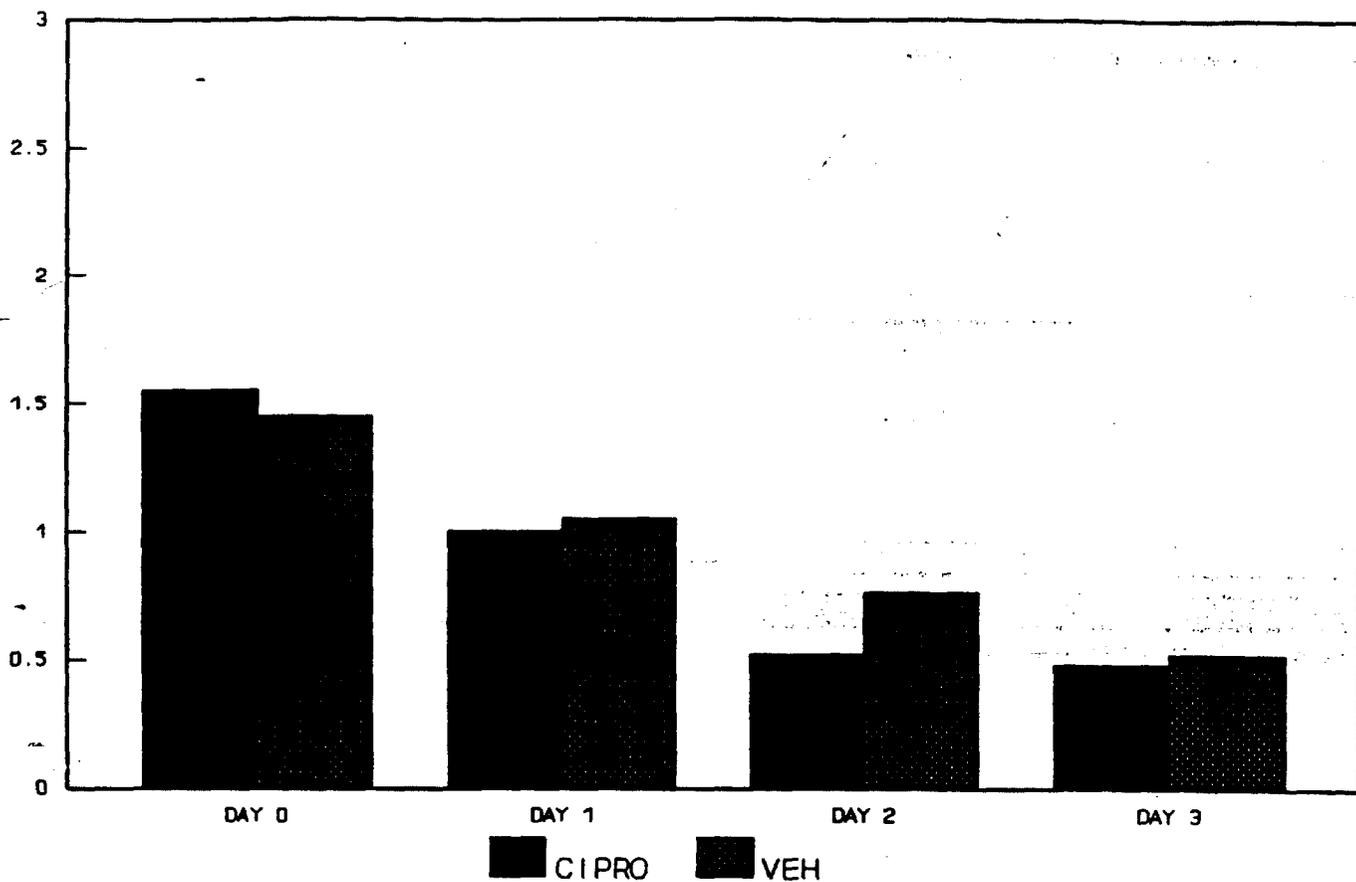
EXUDATION

MEAN SCORES



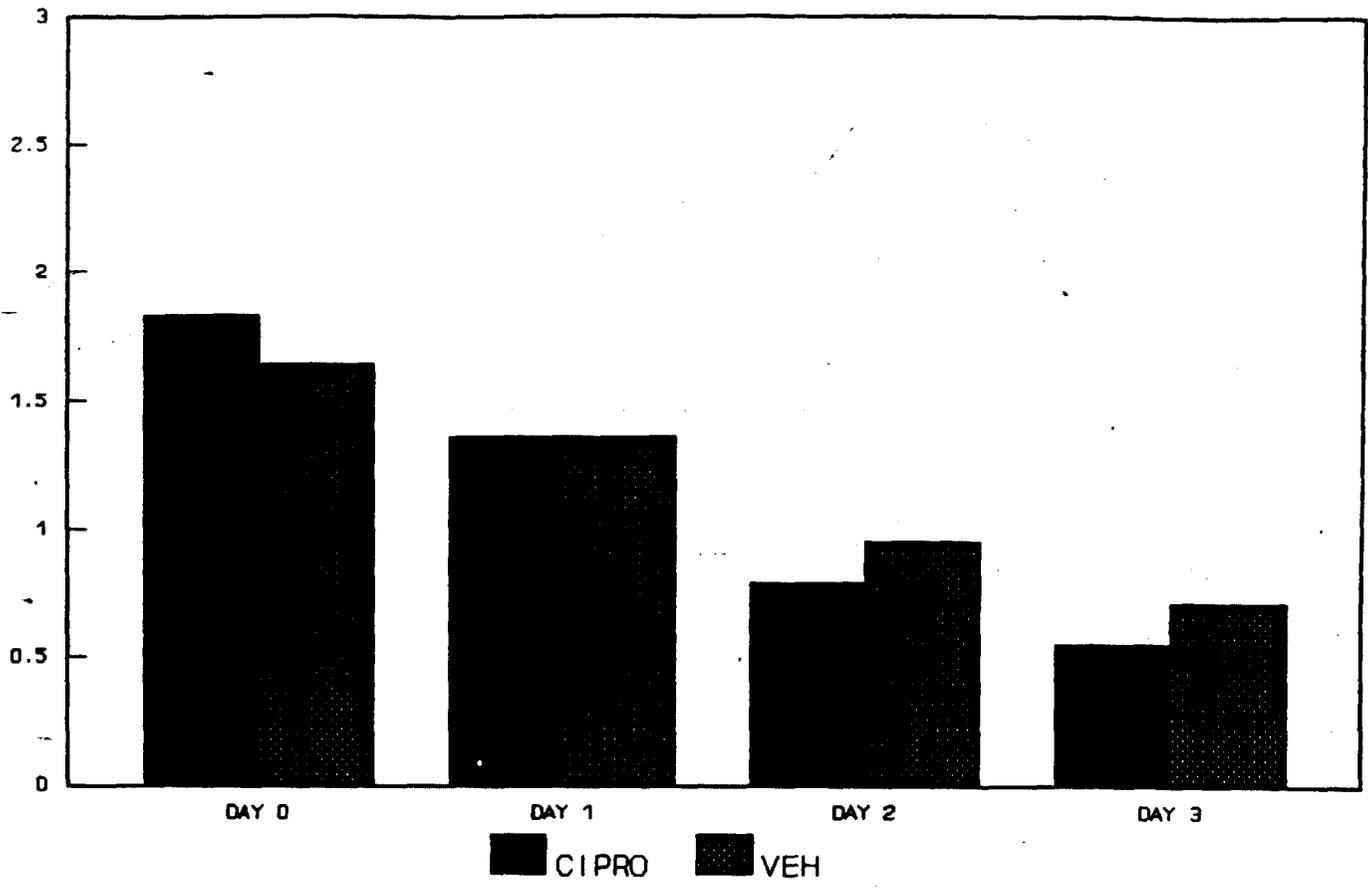
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BULBAR CONJUNCTIVAL INFLAMMATION MEAN SCORES



APPEARS THIS WAY
ON ORIGINAL

PALPEBRAL CONJUNCTIVAL INFLAMMATION MEAN SCORES



Reviewer's Comments: No statistically significant treatment difference was found in the primary clinical efficacy parameters.

APPEARS THIS WAY
ON ORIGINAL

SAFETY

Frequency and Incidence of Medical Events

C-88-94

Coded Medical Events	Ciprofloxacin Ophthalmic Ointment 0.3% N = 70		Placebo (Ciprofloxacin Ophthalmic Ointment Vehicle) N = 74	
	N	%	N	%
Ocular				
Hypemia	1	1.4	2	2.7
Discomfort	1	1.4	1	1.4
Photophobia	1	1.4	2	2.7
Pain	1	1.4	0	
Tearing	1	1.4	0	
Pruritus	1	1.4	1	1.4
Keratoconjunctivitis	1	1.4	0	
Blurred Vision	0		4	5.4
Infiltrate	0		1	1.4
Erythema	0		1	1.4
Discharge NOS	0		1	1.4
Dry Eye	0		1	1.4
Hordeolum	0		1	1.4

APPEARS THIS WAY
ON ORIGINAL

continued

Medical Events	Ciprofloxacin Ophthalmic Ointment 0.3% N = 70		Placebo (Ciprofloxacin Ophthalmic Ointment Vehicle) N = 74	
<u>Nonocular</u>				
<u>Body as a Whole</u> Edema Face	1	1.4	0	
<u>Metabolic and Nutritional</u> Dehydration	1	1.4	0	
<u>Respiratory</u> Bronchitis	1	1.4	0	
Pharyngitis	0		1	1.4
<u>Urogenital</u> Dysmenorrhea	1	1.4	0	

Ciprofloxacin 0.3% Ophthalmic Ointment was evaluated for safety in 70 patients with clinically diagnosed acute bacterial conjunctivitis. Ocular events were infrequent and nonserious. No serious event was reported, and no patient was discontinued from the study due to a serious treatment-related event.

Visual Acuity

Change in Visual Acuity (Snellen Lines)	No Change or Improvement	One Line Decrease	Two Line Decrease	Greater Than a Two Line Decrease	Not Available
Ciprofloxacin 0.3% N = 70	35	10	4	1	20
Placebo N = 74	36	12	4	3	19
TOTAL	71	22	8	4	39

Reviewer's Comments: *No difference in visual acuity was observed between Ciprofloxacin 0.3% Ophthalmic Ointment and placebo (Ciprofloxacin Ophthalmic Ointment vehicle). Blurring due to ointment is likely to be equal in both groups. 25% of the subjects did not have evaluations.*

APPEARS THIS WAY
ON ORIGINAL

Discussion:

Statistical analysis of the two clinical parameters detected no significant differences for patients on ciprofloxacin versus those on placebo. Ciprofloxacin and placebo were not significantly different in the physician's judgment of the clinical resolution of the patients' diseased eyes ($p = 0.34$). The sponsor explanation for these results was that one investigator rated all of his ciprofloxacin and placebo patients as cured, but microbiological data for six of the placebo patients showed the bacteria involved either persisted or proliferated by the end of treatment. Due to this lack of agreement, they considered investigator 1523 as an outlier and an analysis was done using data from the nine other investigators. By this analysis, ciprofloxacin was significantly ($p = 0.02$) better than placebo. The resolution of the cardinal sign palpebral conjunctival inflammation responded significantly better ($p = 0.01$) to ciprofloxacin than to placebo on Day 2.

Despite the fact that the sponsor claims having the power to detect a significant difference between the study groups, excluding the investigator contributing one third of the patients in this study renders the study inadequate.

The study should be repeated in order to be considered supportive of its indication.

APPEARS THIS WAY
ON ORIGINAL

Protocol C-88-24

This study was a randomized, controlled, double-masked and multi-center comparison of the efficacy and safety of Ciprofloxacin Ophthalmic Ointment 0.3% and TOBREX Ophthalmic Ointment (Tobramycin, 0.3%). Forty-six investigators in 27 cities participated in this multiclinic evaluation.

Ciprofloxacin Ophthalmic Ointment 0.3% was compared to TOBREX Ophthalmic Ointment for the treatment of acute bacterial conjunctivitis. Twenty-eight (28) investigators enrolled a total of 500 patients, of which 497 patients were diagnosed with acute bacterial conjunctivitis and included in the intent-to-treat group for statistical analysis of the drugs' clinical efficacies (244 Ciprofloxacin patients and 253 TOBREX patients). Of this group, 178 patients (87 Ciprofloxacin patients and 91 TOBREX patients) were evaluative for antibacterial and clinical efficacies and were analyzed separately from the intent-to-treat group.

If the patient was eligible for the study based on inclusion and exclusion criteria, the study details were explained and a signed and witnessed informed consent was obtained. A history of each patient was obtained, an ocular exam performed, and ocular signs and symptoms were recorded. An entrance pregnancy test was administered to female patients if they were not postmenopausal, had a hysterectomy, a bilateral oophorectomy or were pre-pubertal.

Bacterial specimens were obtained from the conjunctiva of each affected eye of each enrolled patient according to the regimen described in the protocol. A method described by Cagle and Abshire was modified and used to quantify the bacteria present in these specimens. These specimens were labeled appropriately and then sent to an approved and validated laboratory for analyses. Conjunctival specimens were designated as either culture-positive or culture-negative for bacteria based on threshold levels defined in the protocol. The threshold criteria for culture-positive specimens were the same as previous study (C-88-94).

The masked medication (ciprofloxacin or tobramycin) was issued to the patient according to a computerized random treatment code. The investigator demonstrated to the patient the procedure for instilling the drug. The patient was instructed to instill a 1/2" ribbon three times a day into each affected eye on Days 0 and 1 and a 1/2" ribbon into each affected eye two times a day on Day 2 through Day 6. In addition, the patient received an instruction sheet containing the dosing information. Dosing was discontinued at 10 p.m. on the night before the second required visit with exam and culture (Day 7 \pm 2 days).

Clinical observation and evaluation of signs and symptoms were performed on Days 0, 3 and 7 (\pm 2 days). The conjunctivae of the affected eye(s) were cultured for bacteria on Days 0 and 7 (\pm 2 days). An optional visit was allowed on Day 3 (\pm 1 day), provided the investigator felt that the patient should be examined during the course of the study; signs and symptoms were evaluated and recorded on this visit but cultures were not obtained.

Conjunctivitis patients were considered to be evaluative for efficacy if they were conjunctival culture-positive on Day 0, dosed the medication for at least six days and returned for their Day 7 (\pm 2 days) follow-up exam and culture. Patients were evaluative for safety if they received at least one dose of medication. Discontinuation of treatment occurred for any of the following reasons: worsening of the disease (two or more signs or symptoms significantly worsened); clinically significant adverse medical event; protocol violation; personal reasons.

The efficacy of Ciprofloxacin Ophthalmic Ointment 0.3% relative to tobramycin was determined by evaluating the criteria: the bacteriological results of the conjunctival specimens at Day 7 (\pm 2 days) relative to Day 0, the physician's clinical judgment at Day 7 (\pm 2 days) regarding overall resolution of disease and severity scores assigned to the five cardinal clinical signs of conjunctivitis. The cardinal signs evaluated were: erythema, exudation, discharge, and palpebral and bulbar conjunctival inflammation. Therefore, bacterial culture results, physician follow-up impression and resolution of the cardinal signs were the major efficacy variables analyzed statistically.

Microbiological efficacy was analyzed statistically by comparing the verdicts of the bacterial cultures obtained on Day 7 relative to those obtained on Day 0. The counts or quantified numbers of microorganisms were classified as "eradicated," "reduced," "persisted," or "proliferated" relative to the Day 0 culture.

These terms are defined as follows:

Verdict	Definition
Eradication (E)	Infection Organism originally present above threshold on Day 0 is absent in follow-up culture.
Reduction (R)	Pathogen originally present above threshold on Day 0 is reduced to a count below threshold in a follow-up culture.
Persistence (NC)	Pathogen originally present above threshold on Day 0 is reduced to a count below Day 0 count, but is above or equal to threshold in follow-up culture.
Proliferation (P)	Pathogen originally present above threshold on Day 0 is increased to a count above Day 0 count in follow-up culture.

Microbiological success was achieved if the offending microorganism isolated on Day 0 was eradicated or reduced below the relative organism threshold level on Day 7.

To statistically compare the microbiological efficacy of ciprofloxacin and placebo, microbiological efficacy scores were assigned on a per patient basis (0 = eradicated, 1 = reduced, 2 = persisted and 3 = proliferated). For unilateral culture-positive patients, microbiological results for the infected eye were used. For bilateral culture positive patients, microbiological efficacy for the "worse eye" was assigned based on the eye that had the least desirable microbiological response to treatment (proliferation = least desirable, eradication = most desirable). Microbiological efficacy scores and microbiological success were statistically analyzed using the Cochran-Mantel-Haenszel Rank Score test.

Clinical observations were made by the investigator on Days 3 (optional visit) and 7 by evaluating the patient's overall clinical condition. The investigator made one of the following judgments regarding the patient's response to therapy at each follow-up visit: Cured (score 0) = absence of signs or symptoms; Better (score 1) = a unit change in two or more signs or symptoms; Unchanged (score 2) = no response in overall change in signs or symptoms; Worse (score 3) = overall increase in signs or symptoms. The scores assigned to the physician's evaluations were statistically evaluated using the Cochran-Mantel-Haenszel Rank Score test.

The scoring of ocular signs and symptoms (minimum, zero - not present; maximum, three -severe) was reflective of the conjunctivitis, not of the transient symptomatology related to instillation of medication. At Days 0, 3 and 7 the investigator assigned the following severity scores to each of the signs and symptoms evaluated: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Scoring standardization was obtained by referring to a manual of definitions which was contained in the Case Report Form. The following ocular symptoms were evaluated: discomfort, acute ocular pain, tearing, photophobia and itching. The ocular signs that were evaluated included: erythema, discharge, exudation, bulbar and palpebral conjunctival inflammation, limbal changes, epithelial disease, focal stromal infiltration, and aqueous reaction (cells and flare).

Reviewer's Comments: *The day 3 visit should not have been optional.*

LIST OF INVESTIGATORS

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
1252	C. Michael Adams, M.D. Omega Eye Care Center Birmingham, AL	01/18/91 - 10/18/91
1140	Yue-Kong Au, M.D. LSU Medical Center Shreveport, LA	02/05/90 - 09/30/91
1044	D. C. Brick, M.D. 490 N. Alvernon Way Tucson, AZ	10/03/89 - 06/28/90
597	Stuart I. Brown, M.D. University Calif. San Diego San Diego, CA	03/03/89 - 05/03/90
1043	David Bryan, M.D. Line Ave., 65 Street Shreveport, LA	03/22/89 - 05/21/90
362	Delmar R. Caldwell, M.D. Tulane Medical School New Orleans, LA	04/15/91 - 10/18/91
1220	Mark Coffman, M.D. Texas Regional Eye Center Bryan, TX	02/19/91 - 10/18/91
1229	James Luther Crabb, M.D. Eye-Tech of Memphis Memphis, TN	11/09/90 - 10/18/91
1052	R. Bruce Grene, M.D. Wichita Eye Foundation Wichita, KS	07/23/90 - 10/18/91
1008	Barry Horwitz, M.D. 8945 Long Point Houston, TX	06/02/89 - 10/18/91

APPEARS THIS WAY
ON ORIGINAL

LIST OF INVESTIGATORS - Continued

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
372	Robert A. Hyndiuk, M.D. Medical College of Wisconsin Milwaukee, WI	05/12/89 - 06/26/90
557	Michael S. Insler, M.D. Louisiana State University Eye Center New Orleans, LA	04/08/91 - 10/18/91
824	Evan D. Jones, M.D. Carolina Eye Center Charleston, SC	04/03/89 - 10/18/91
*943	Robert A. Laibovitz, M.D. 3307 Northland Dr. Austin, TX	03/29/89 - 11/03/89
1037	Michael Lamensdorf, M.D. 1950 Arlington St. Sarasota, FL	03/22/89 - 10/18/91
1123	Michael Limberg, M.D. 1457 Marsh St. San Luis Obispo, CA	05/09/90 - 10/18/91
1045	Gary Mackman, M.D. 777 E. Brill St. Phoenix, AZ	05/03/89 - 06/27/90
331	Alan I. Mandell, M.D. St. Francis Professional Bldg. 6005 Park Ave., Suite 926-B Memphis, TN	06/11/90 - 08/05/91
1025	Peter J. McDonnell, M.D. USC-Doheny Eye Institute Los Angeles, CA	03/02/89 - 05/02/90

* Investigator in study C-88-24

APPEARS THIS WAY
ON ORIGINAL

LIST OF INVESTIGATORS - Continued

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
984	Charles Moore, M.D. International Eye Care Association Houston, TX	01/20/89 - 11/09/89
750	Kenneth Olander, M.D. Eye Physician Associates 2040 W. Wisconsin Ave. Milwaukee, WI	05/16/91 - 10/18/91
524	Randall Olson, M.D. University of Utah Medical Center Salt Lake City, UT	01/28/91 - 10/18/91
978	Charles Ostrov, M.D. 4001 Stinson Blvd., N.E. Minneapolis, MN	05/08/90 - 10/18/91
1195	Peter Rapoza, M.D. 2880 University Ave. Madison, WI	10/24/90 - 10/18/91
1196	Robert Rice, M.D. McGuire Clinic Richmond, VA	10/17/90 - 10/18/91
354	J. James Rowsey, M.D. McGee Eye Institute Oklahoma City, OK	09/28/89 - 10/02/91
635	David Schanzlin, M.D. Bethesda Eye Institute St. Louis, MO	04/06/90 - 10/18/91
1110	Neal Sher, M.D. Medical Arts Bldg. Minneapolis, MN	05/08/90 - 10/18/91

APPEARS THIS WAY
ON ORIGINAL

LIST OF INVESTIGATORS - Continued

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
316	Gilbert Smolin, M.D. 931 W. San Bruno Ave. San Bruno, CA	04/02/89 - 05/01/90
1112	Robert Snyder, M.D., Ph.D. University Arizona HSC Tucson, AZ	01/10/90 - 09/18/91
861	Saul Ullman, M.D. Medical Center Clinic, P.A. Pensacola, FL	07/26/89 - 10/18/91
1240	R. Roy Whitaker, M.D. Dallas Medical & Surgical Group Dallas, TX	11/01/90 - 10/18/91
1001	A. Thomas Williams, M.D. Rocky Mountain Eye Center Salt Lake City, UT	07/26/90 - 10/18/91
798	Richard W. Yee, M.D. UTHSC - San Antonio San Antonio, TX	08/16/89 - 10/18/91
1117	Ralph W. Zabel, M.D. Park Ave. Med. Bldg. Minneapolis, MN	06/06/90 - 02/20/91

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RESULTS:

Patient Populations - Evaluabilities

Treatment	Enrolled	Evaluative for		Nonevaluative for Efficacy
		Safety	Efficacy	
Ciprofloxacin	246	244	87	157
Tobramycin	254	253	91	162
Total	500*	497 ¹	178 ²	319

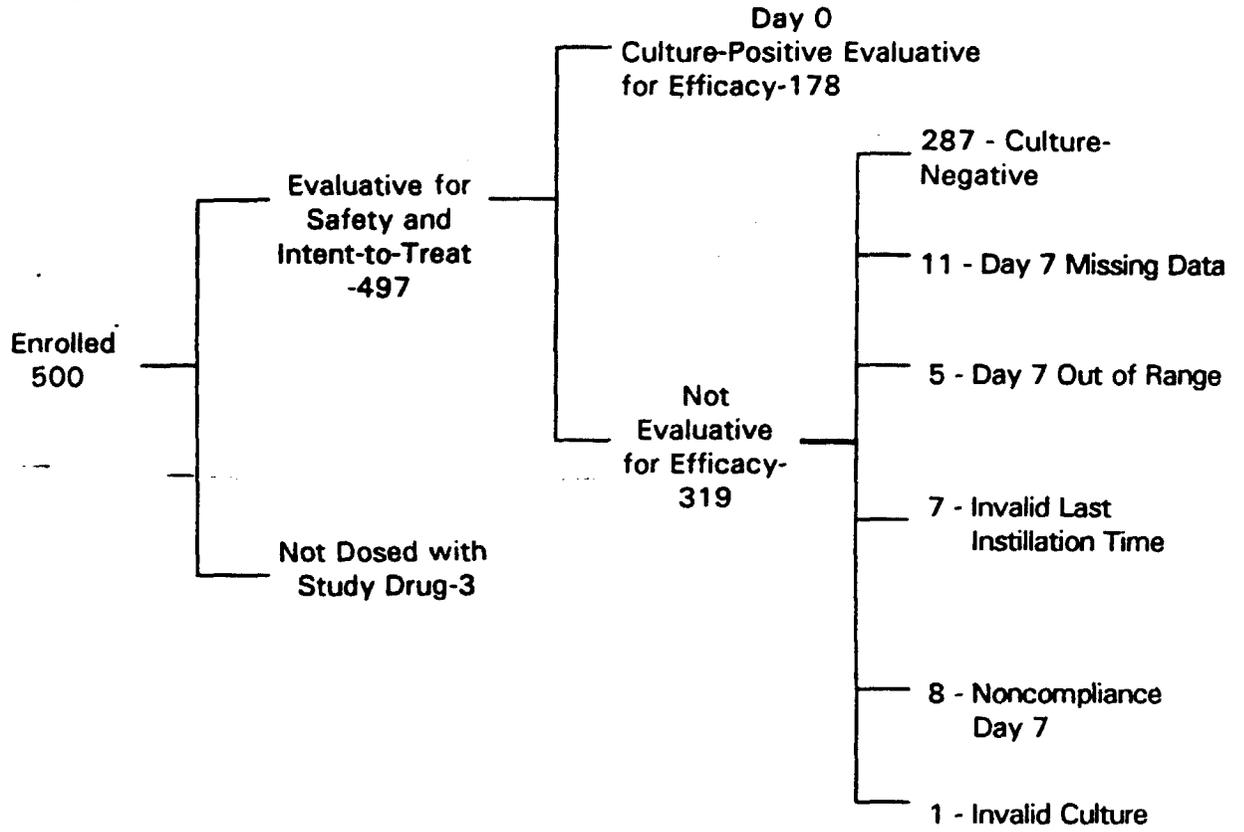
¹Intent-to-treat group.

²Culture-positive evaluative group.

*Three patients withdrew themselves and were not dosed with study drug (Ciprofloxacin [2], 1203, 1905; Tobramycin [1], 2003).

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ON ORIGINAL

Distribution of Patients



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Distribution of Enrolled Patients by Investigator

	Enrolled ¹		Efficacy ²	
	TREATMENT		TREATMENT	
	TOBREX	CIPROFLOXACIN OINT	TOBREX	CIPROFLOXACIN OINT
Investigator				
331 MANDELL, ALAN I.	2	2	1	1
354 ROWSEY, JAMES J.	6	*5	2	.
362 CALDWELL, DELMAR R.	6	6	2	1
524 OLSON, RANDALL J.	11	10	5	5
557 INSLER, MICHAEL S.	8	6	1	2
635 SCHANZLIN, DAVID J.	10	10	3	3
798 YEE, RICHARD W.	3	4	.	1
824 JONES, EVAN D.	3	2	1	.
861 ULLMAN, SAUL	20	20	7	8
943 LAIBOVITZ, ROBERT A.	24	24	11	8
978 OSTROV, CHARLES C.	6	7	2	2
984 MOORE, CHARLES R.	2	2	.	.
1001 WILLIAMS, A. THOMAS	12	12	2	4
1008 HORWITZ, BARRY	48	48	19	17
1025 MCDONNELL, PETER J.	1	1	1	1
1037 LAMENSDORF, MICHAEL	21	19	8	6

Continued . . .

APPEARS THIS WAY
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Continued

	Enrolled ¹		Efficacy ²	
	TREATMENT		TREATMENT	
	TOBREX	CIPROFLOXACIN OINT	TOBREX	CIPROFLOXACIN OINT
Investigator				
1046 SNYDER, DAVID A.	7	6	1	3
1052 GRENE, R. BRUCE	1	1	1	1
1110 SHER, NEAL A.	13	11	5	7
1112 SNYDER, ROBERT	3	*3	2	1
1123 LIMBERG, MICHAEL B.	3	2	.	1
1140 AU, YUE/KONG	*8	9	1	.
1195 RAPOZA, PETER	3	3	1	2
1196 RICE, ROBERT	2	1	.	1
1220 COFFMAN, MARK R.	2	3	.	.
1229 CRABB, JAMES LUTHER	20	20	12	9
1240 WHITAKER, ROY (ROBERT)	2	2	2	.
1252 ADAMS, MICHAEL C.	7	7	1	3
TOTAL	254 *(253)	246 *(244)	91	87

¹Intent-to-Treat group (this group was also evaluated for safety).

²Culture-positive evaluative group.

*Three patients were enrolled, but did not receive drug or were never dosed.

APPEARS THIS WAY
ON ORIGINAL

DEMOGRAPHICS

Demographics for Culture-Positive Evaluative Patients

	AGE			
	N	MEAN	STD	RANGE
TOBREX	91	51.65	23.14	5-94
Cipro	87	45.78	22.96	2-85

p=0.09, Two-sample t-test

	SEX					
	TOTAL	MALE		FEMALE		
		N	%	N	%	
TOBREX	91	37	40.66	54	59.34	
Cipro	87	45	51.72	42	48.28	

p=0.14, Chi-square test for independence

	RACE									
	TOTAL	WHITE		BLACK		AM IND		HISP		
		N	%	N	%	N	%	N	%	
TOBREX	91	74	81.32	14	15.38	-	-	3	3.30	
Cipro	87	75	86.21	7	8.05	1	1.15	4	4.60	

p=0.92, Chi-square test for independence

Reviewer's Comments: *No significant treatment differences were found for any of the demographic characteristics of the culture-positive patients evaluative for efficacy.*

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Demographics for Intent-to-Treat Patients

AGE

	N	MEAN	STD	RANGE
TOBREX	253	46.4	21.81	3-94
Cipro	244	44.6	22.16	2-93

p=0.36, Two-sample t-test

SEX

	TOTAL	MALE		FEMALE	
		N	%	N	%
TOBREX	253	101	39.9	152	60.1
Cipro	244	111	45.5	133	54.5

p=0.21, Chi-square test for independence

RACE

	TOTAL	WHITE		BLACK		ASIAN		AM IND		HISP		OTHER	
		N	%	N	%	N	%	N	%	N	%	N	%
TOBREX	253	198	78.3	40	15.8	2	0.8	-	-	13	5.1	-	-
Cipro	244	189	77.5	39	16.0	-	-	2	0.8	11	4.5	3	1.2

p=0.60, Chi-square test for independence

Reviewer's Comments: *No significant differences were observed in the demographics by treatment within the intent-to-treat group.*

APPEARS THIS WAY
ON ORIGINAL

Involved Eye for Culture-Positive Evaluative Patients

	TOTAL	OD		OS		OU	
		N	%	N	%	N	%
TOBREX	91	26	28.6	20	22.0	45	49.5
Cipro	87	22	25.3	20	23.0	45	51.7

p=0.66, Chi-square test for independence

Involved Eye for Intent-To-Treat Patients

	TOTAL	OD		OS		OU	
		N	%	N	%	N	%
TOBREX	253	64	25.3	75	29.6	114	45.1
Cipro	244	76	31.1	59	24.2	109	44.7

p=0.41, Chi-square test for independence

APPEARS THIS WAY -
ON ORIGINAL

Duration of Ocular Disease for Culture-Positive Patients

	N	MEAN	STD	RANGE
TOBREX	91	8.0	8.98	
Cipro	87	6.1	6.84	

p=0.11, Two-sample t-test

Reviewer's Comments: *No statistical differences within the two treatment groups were discernible.*

Duration of Ocular Disease for Intent-to-Treat Patients

	N	MEAN	STD	RANGE
TOBREX	253	9.7	22.32	
Cipro	243	10.9	48.57	

p=0.72, Two-sample t-test

Reviewer's Comments: *Why were patients with conjunctivitis for 2 years enrolled?*

**APPEARS THIS WAY
ON ORIGINAL**

Days on Treatment for Culture-Positive Evaluative Patients

	N	MEAN	STD	RANGE
TOBREX	91	7.0	0.49	
Cipro	87	7.0	0.57	

p=0.40, Two-sample t-test

Days on Treatment for Intent-to-Treat Patients

	N	MEAN	STD	RANGE
TOBREX	247	6.9	1.31	
Cipro	233	7.0	1.04	

p=0.57, Two-sample t-test

Reviewer's Comments: *Treatment comparisons for days on treatment indicate no significant differences in either the culture-positive group ($p = 0.40$) or the intent-to-treat group ($p = 0.57$).*

EFFICACY:

MICROBIOLOGY

Evaluative Patients - Microbiological and Clinical Results
A. TOBREX - Treated Patients

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0331	2501	<i>Staphylococcus epidermidis</i>	Eradication	Cured
0354	1208	<i>Staphylococcus aureus</i>	Eradication	Cured
	1210	<i>Staphylococcus aureus</i>	Eradication	Cured
0362	5005	<i>Staphylococcus aureus</i>	Eradication	Cured
	5011	<i>Staphylococcus aureus</i>	Reduction	Cured
0524	3503	<i>Staphylococcus aureus</i>	Reduction	Cured
		<i>Staphylococcus epidermidis</i>		
	3508	<i>Staphylococcus epidermidis</i>	Reduction	Unchanged
	3516	<i>Haemophilus sp.</i>	Eradication	Better
	3518	<i>Staphylococcus epidermidis</i>	Reduction	Cured
3521	<i>Coagulase-negative Staphylococcus sp.</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus sp.</i>	Persistence	Cured	
0557	6003	<i>Micrococcus sp.</i> <i>Moraxella sp.</i> <i>Bacillus sp.</i>	Eradication	Unchanged
0635	1802	<i>Staphylococcus aureus</i>	Eradication	Better
	1807	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	1809	<i>Staphylococcus epidermidis</i> <i>Klebsiella sp.</i>	Proliferation	Cured
0824	0211	<i>Staphylococcus aureus</i>	Eradication	Cured
0861	1707	<i>Staphylococcus epidermidis</i>	Eradication	Better
	1710	<i>Haemophilus influenzae</i>	Proliferation	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0861	1714	<i>Serratia marcescens</i> <i>Acinetobacter sp.</i> <i>Pseudomonas sp.</i>	Eradication	Unchanged
	1716	<i>Micrococcus sp.</i>	Eradication	Cured
	1719	<i>Staphylococcus aureus</i>	Eradication	Cured
	1724	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1728	<i>Streptococcus sp.</i> <i>Klebsiella sp.</i> <i>Serratia marcescens</i>	Eradication	Cured
0943	1307	<i>Haemophilus aegyptius</i>	Eradication	Cured
	1311	<i>Staphylococcus epidermidis</i> <i>Micrococcus sp.</i>	Reduction	Better
	1314	Coagulase-negative <i>Staphylococcus sp.</i>	Reduction	Better
	1315	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	1318	<i>Staphylococcus aureus</i>	Eradication	Cured
	1319	Coagulase-negative <i>Staphylococcus sp.</i> <i>Acinetobacter sp.</i>	Eradication	Cured
	1324	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1339	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i> <i>Proteus/Morganella sp.</i> <i>Acinetobacter sp.</i> <i>Corynebacterium sp.</i> <i>Enterobacteriaceae sp.</i>	Persistence	Better
	1342	<i>Staphylococcus aureus</i>	Eradication	Better
	1344	<i>Staphylococcus epidermidis</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0943	1346	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i>	Reduction	Cured
0978	2117	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	2121	<i>Staphylococcus aureus</i>	Eradication	Cured
1001	2812	<i>Acinetobacter sp.</i>	Eradication	Cured
	2817	<i>Streptococcus pneumoniae</i>	Persistence	Cured
1008	1510	<i>Staphylococcus aureus</i>	Eradication	Cured
	1511	<i>Staphylococcus epidermidis</i>	Eradication	Better
	1520	<i>Haemophilus influenzae</i>	Eradication	Better
	1525	<i>Serratia marcescens</i>	Eradication	Cured
	1542	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Better
	1547	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	1548	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	2607	<i>Staphylococcus epidermidis</i>	Reduction	Better
	2612	<i>Staphylococcus aureus</i>	Eradication	Cured
	2613	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	2618	<i>Streptococcus sp.</i>	Eradication	Better
	2621	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Persistence	Better
	2622	<i>Staphylococcus aureus</i> Coagulase-negative <i>Staphylococcus sp.</i>	Eradication	Cured
	2625	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> Coagulase-negative <i>Staphylococcus sp.</i>	Reduction	Cured
	2628	<i>Staphylococcus aureus</i>	Persistence	Better

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
1008	2629	<i>Haemophilus sp.</i>	Eradication	Cured
	2634	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Reduction	Cured
	2639	<i>Pseudomonas sp.</i>	Eradication	Cured
	2648	<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i>	Reduction	Cured
1025	0502	<i>Haemophilus influenzae</i>	Eradication	Cured
1037	1105	<i>Staphylococcus aureus</i>	Eradication	Better
	1108	<i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Cured
	1113	<i>Staphylococcus aureus</i>	Eradication	Cured
	1116	<i>Staphylococcus aureus</i>	Eradication	Cured
	1129	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i>	Persistence	Cured
	1133	<i>Haemophilus sp.</i>	Eradication	Cured
	1134	<i>Staphylococcus aureus</i>	Eradication	Cured
	1138	<i>Staphylococcus epidermidis</i>	Eradication	Cured
1046	1004	<i>Staphylococcus epidermidis</i> <i>Proteus/Morganella sp.</i>	Reduction	Cured
1052	2702	<i>Staphylococcus aureus</i>	Proliferation	Cured
1110	2303	<i>Streptococcus sp.</i>	Eradication	Cured
	2310	<i>Haemophilus influenzae</i>	Eradication	Cured
	2311	<i>Staphylococcus aureus</i>	Eradication	Cured
	2325	<i>Pseudomonas sp.</i>	Eradication	Cured
	2328	<i>Streptococcus pneumoniae</i>	Eradication	Cured
1112	1901	<i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Cured
	1904		Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
1140	2011	<i>Streptococcus pneumoniae</i>	Eradication	Cured
1195	2908	<i>Pseudomonas sp.</i>	Eradication	Cured
1229	3102	<i>Staphylococcus epidermidis</i>	Eradication	Better
	3103	<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i>	Eradication	Cured
	3111	<i>Staphylococcus epidermidis</i>	Persistence	Unchanged
	3113	<i>Staphylococcus aureus</i>	Eradication	Better
	3119	<i>Staphylococcus epidermidis</i>	Persistence	Unchanged
	3121	<i>Staphylococcus aureus</i>	Reduction	Better
	3127	<i>Staphylococcus epidermidis</i> <i>Haemophilus influenzae</i>	Eradication	Cured
	3129	<i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Better
	3131	<i>Streptococcus pneumoniae</i>	Eradication	Better
	3133	<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i>	Eradication	Better
	3138	<i>Staphylococcus epidermidis</i>	Reduction	Unchanged
3139	<i>Staphylococcus aureus</i>	Proliferation	Worse	
1240	3202	<i>Staphylococcus aureus</i>	Eradication	Cured
	3203	<i>Proteus/Morganella sp.</i>	Eradication	Cured
1252	3410	<i>Streptococcus sp.</i>	Eradication	Cured

B. Ciprofloxacin - Treated Patients

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
0331	2504	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Better
0362	5001	<i>Haemophilus influenzae</i>	Eradication	Cured
0524	3506	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Better
	3507	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Better
	3512	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	3515	<i>Staphylococcus aureus</i>	Reduction	Cured
	3520	<i>Streptococcus pneumoniae</i> <i>Haemophilus sp.</i>	Eradication	Cured
0557	6004	<i>Staphylococcus aureus</i>	Reduction	Cured
	6009	<i>Acinetobacter sp.</i>	Eradication	Cured
0635	1804	<i>Staphylococcus epidermidis</i>	Eradication	Better
	1810	<i>Haemophilus influenzae</i>	Eradication	Cured
	1811	<i>Staphylococcus aureus</i>	Eradication	Better
0798	0605	<i>Staphylococcus epidermidis</i>	Eradication	Better
0861	1715	<i>Haemophilus influenzae</i>	Eradication	Cured
	1717	<i>Haemophilus influenzae</i>	Eradication	Better
	1720	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	1725	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
	1727	<i>Haemophilus influenzae</i>	Eradication	Cured
	1730	<i>Staphylococcus aureus</i>	Eradication	Better

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
	1736	<i>Streptococcus sp.</i> <i>Klebsiella sp.</i>	Eradication	Better
	1737	<i>Staphylococcus aureus</i>	Eradication	Cured
0943	1308	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Reduction	Cured
	1320	<i>Staphylococcus epidermidis</i> <i>Klebsiella sp.</i>	Eradication	Cured
	1321	<i>Acinetobacter sp.</i>	Eradication	Cured
	1327	<i>Bacillus sp.</i>	Eradication	Cured
	1329	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1335	<i>Staphylococcus aureus</i> <i>Corynebacterium sp.</i>	Eradication	Better
	1337	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
	1343	<i>Staphylococcus aureus</i>	Persistence	Cured
0978	2119	<i>Streptococcus pyogenes</i>	Eradication	Cured
	2123	<i>Haemophilus influenzae</i>	Eradication	Cured
1001	2802	<i>Acinetobacter sp.</i>	Eradication	Cured
	2805	<i>Staphylococcus epidermidis</i>	Eradication	Better
	2815	<i>Coagulase-negative Staphylococcus sp.</i> <i>Streptococcus sp.</i>	Eradication	Better
	2823	<i>Moraxella catarrhalis</i> <i>Haemophilus influenzae</i>	Eradication	Cured
1008	1501	<i>Staphylococcus aureus</i>	Eradication	Cured
	1506	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	1508	<i>Acinetobacter sp.</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
1008	1509	<i>Staphylococcus aureus</i> <i>Proteus/Morganella sp.</i>	Eradication	Cured
	1512	<i>Streptococcus sp.</i> <i>Enterobacter sp.</i>	Eradication	Cured
	1516	<i>Staphylococcus aureus</i> <i>Acinetobacter sp.</i>	Eradication	Cured
	1533	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	1541	<i>Streptococcus pneumoniae</i>	Proliferation	Cured
	1544	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	2606	<i>Staphylococcus epidermidis</i> <i>Acinetobacter sp.</i>	Reduction	Cured
	2609	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i>	Eradication	Cured
	2614	<i>Staphylococcus epidermidis</i> <i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Better
	2619	<i>Coagulase-negative Staphylococcus sp.</i> <i>Haemophilus influenzae</i>	Eradication	Cured
	2620	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
	2623	<i>Staphylococcus aureus</i>	Eradication	Cured
	2638	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	2646	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
1025	0501	<i>Haemophilus influenzae</i>	Eradication	Better
1037	1101	<i>Streptococcus sp.</i>	Eradication	Better
	1106	<i>Staphylococcus aureus</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
1037	1115	<i>Staphylococcus epidermidis</i> <i>Coagulase-negative Staphylococcus sp.</i>	Reduction	Better
	1121	<i>Streptococcus sp.</i>	Eradication	Cured
	1127	<i>Micrococcus sp.</i>	Eradication	Cured
	1128	<i>Haemophilus influenzae</i>	Eradication	Cured
1046	1003	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1005	<i>Staphylococcus epidermidis</i>	Reduction	Better
	1009	<i>Staphylococcus aureus</i>	Eradication	Better
1052	2701	<i>Staphylococcus aureus</i>	Eradication	Better
1110	2301	<i>Staphylococcus aureus</i>	Eradication	Cured
	2302	<i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Cured
	2305	<i>Haemophilus influenzae</i>	Eradication	Cured
	2307	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	2327	<i>Staphylococcus aureus</i>	Eradication	Cured
	2332	<i>Staphylococcus aureus</i>	Eradication	Cured
	2348	<i>Staphylococcus aureus</i>	Eradication	Cured
1112	1902	<i>Streptococcus pneumoniae</i>	Eradication	Better
1123	2405	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
1195	2902	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	2905	<i>Streptococcus pneumoniae</i>	Eradication	Cured
1196	3003	<i>Staphylococcus epidermidis</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
1229	3101	<i>Staphylococcus epidermidis</i>	Eradication	Better
	3104	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	3108	<i>Staphylococcus aureus</i>	Eradication	Cured
	3109	<i>Staphylococcus epidermidis</i> <i>Haemophilus influenzae</i>	Eradication	Cured
	3118	<i>Staphylococcus aureus</i>	Eradication	Unchanged
	3123	<i>Staphylococcus aureus</i>	Eradication	Cured
	3124	<i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Cured
	3126	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	3140	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Reduction	Cured
1252	3402	<i>Staphylococcus aureus</i>	Eradication	Cured
	3405	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	3413	<i>Acinetobacter sp.</i>	Persistence	Cured

Evaluative Patients - Microbiological and Clinical Results
A. TOBEX - Treated Patients

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0331	2501	<i>Staphylococcus epidermidis</i>	Eradication	Cured
0354	1208	<i>Staphylococcus aureus</i>	Eradication	Cured
	1210	<i>Staphylococcus aureus</i>	Eradication	Cured
0362	5005	<i>Staphylococcus aureus</i>	Eradication	Cured
	5011	<i>Staphylococcus aureus</i>	Reduction	Cured
0524	3503	<i>Staphylococcus aureus</i>	Reduction	Cured
		<i>Staphylococcus epidermidis</i>		
	3508	<i>Staphylococcus epidermidis</i>	Reduction	Unchanged
	3516	<i>Haemophilus sp.</i>	Eradication	Better
	3518	<i>Staphylococcus epidermidis</i>	Reduction	Cured
3521	<i>Coagulase-negative Staphylococcus sp.</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus sp.</i>	Persistence	Cured	
0557	6003	<i>Micrococcus sp.</i> <i>Moraxella sp.</i> <i>Bacillus sp.</i>	Eradication	Unchanged
0635	1802	<i>Staphylococcus aureus</i>	Eradication	Better
	1807	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	1809	<i>Staphylococcus epidermidis</i> <i>Klebsiella sp.</i>	Proliferation	Cured
0824	0211	<i>Staphylococcus aureus</i>	Eradication	Cured
0861	1707	<i>Staphylococcus epidermidis</i>	Eradication	Better
	1710	<i>Haemophilus influenzae</i>	Proliferation	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0861	1714	<i>Serratia marcescens</i> <i>Acinetobacter sp.</i> <i>Pseudomonas sp.</i>	Eradication	Unchanged
	1716	<i>Micrococcus sp.</i>	Eradication	Cured
	1719	<i>Staphylococcus aureus</i>	Eradication	Cured
	1724	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1728	<i>Streptococcus sp.</i> <i>Klebsiella sp.</i> <i>Serratia marcescens</i>	Eradication	Cured
0943	1307	<i>Haemophilus aegyptius</i>	Eradication	Cured
	1311	<i>Staphylococcus epidermidis</i> <i>Micrococcus sp.</i>	Reduction	Better
	1314	Coagulase-negative <i>Staphylococcus sp.</i>	Reduction	Better
	1315	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	1318	<i>Staphylococcus aureus</i>	Eradication	Cured
	1319	Coagulase-negative <i>Staphylococcus sp.</i> <i>Acinetobacter sp.</i>	Eradication	Cured
	1324	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1339	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i> <i>Proteus/Morganella sp.</i> <i>Acinetobacter sp.</i> <i>Corynebacterium sp.</i> <i>Enterobacteriaceae sp.</i>	Persistence	Better
	1342	<i>Staphylococcus aureus</i>	Eradication	Better
	1344	<i>Staphylococcus epidermidis</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
0943	1346	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i>	Reduction	Cured
0978	2117	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	2121	<i>Staphylococcus aureus</i>	Eradication	Cured
1001	2812	<i>Acinetobacter sp.</i>	Eradication	Cured
	2817	<i>Streptococcus pneumoniae</i>	Persistence	Cured
1008	1510	<i>Staphylococcus aureus</i>	Eradication	Cured
	1511	<i>Staphylococcus epidermidis</i>	Eradication	Better
	1520	<i>Haemophilus influenzae</i>	Eradication	Better
	1525	<i>Serratia marcescens</i>	Eradication	Cured
	1542	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Better
	1547	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	1548	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	2607	<i>Staphylococcus epidermidis</i>	Reduction	Better
	2612	<i>Staphylococcus aureus</i>	Eradication	Cured
	2613	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	2618	<i>Streptococcus sp.</i>	Eradication	Better
	2621	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Persistence	Better
	2622	<i>Staphylococcus aureus</i> Coagulase-negative <i>Staphylococcus sp.</i>	Eradication	Cured
	2625	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> Coagulase-negative <i>Staphylococcus sp.</i>	Reduction	Cured
2628	<i>Staphylococcus aureus</i>	Persistence	Better	

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
1008	2629	<i>Haemophilus sp.</i>	Eradication	Cured
	2634	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Reduction	Cured
	2639	<i>Pseudomonas sp.</i>	Eradication	Cured
	2648	<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i>	Reduction	Cured
1025	0502	<i>Haemophilus influenzae</i>	Eradication	Cured
1037	1105	<i>Staphylococcus aureus</i>	Eradication	Better
	1108	<i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Cured
	1113	<i>Staphylococcus aureus</i>	Eradication	Cured
	1116	<i>Staphylococcus aureus</i>	Eradication	Cured
	1129	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i>	Persistence	Cured
	1133	<i>Haemophilus sp.</i>	Eradication	Cured
	1134	<i>Staphylococcus aureus</i>	Eradication	Cured
	1138	<i>Staphylococcus epidermidis</i>	Eradication	Cured
1046	1004	<i>Staphylococcus epidermidis</i> <i>Proteus/Morganella sp.</i>	Reduction	Cured
1052	2702	<i>Staphylococcus aureus</i>	Proliferation	Cured
1110	2303	<i>Streptococcus sp.</i>	Eradication	Cured
	2310	<i>Haemophilus influenzae</i>	Eradication	Cured
	2311	<i>Staphylococcus aureus</i>	Eradication	Cured
	2325	<i>Pseudomonas sp.</i>	Eradication	Cured
	2328	<i>Streptococcus pneumoniae</i>	Eradication	Cured
1112	1901	<i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Cured
	1904	<i>Bacillus sp.</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgment
1140	2011	<i>Streptococcus pneumoniae</i>	Eradication	Cured
1195	2908	<i>Pseudomonas sp.</i>	Eradication	Cured
1229	3102	<i>Staphylococcus epidermidis</i>	Eradication	Better
	3103	<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i>	Eradication	Cured
	3111	<i>Staphylococcus epidermidis</i>	Persistence	Unchanged
	3113	<i>Staphylococcus aureus</i>	Eradication	Better
	3119	<i>Staphylococcus epidermidis</i>	Persistence	Unchanged
	3121	<i>Staphylococcus aureus</i>	Reduction	Better
	3127	<i>Staphylococcus epidermidis</i> <i>Haemophilus influenzae</i>	Eradication	Cured
	3129	<i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Better
	3131	<i>Streptococcus pneumoniae</i>	Eradication	Better
	3133	<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i>	Eradication	Better
	3138	<i>Staphylococcus epidermidis</i>	Reduction	Unchanged
3139	<i>Staphylococcus aureus</i>	Proliferation	Worse	
1240	3202	<i>Staphylococcus aureus</i>	Eradication	Cured
	3203	<i>Proteus/Morganella sp.</i>	Eradication	Cured
1252	3410	<i>Streptococcus sp.</i>	Eradication	Cured

B. Ciprofloxacin - Treated Patients

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
0331	2504	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Better
0362	5001	<i>Haemophilus influenzae</i>	Eradication	Cured
0524	3506	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Better
	3507	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Better
	3512	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	3515	<i>Staphylococcus aureus</i>	Reduction	Cured
	3520	<i>Streptococcus pneumoniae</i> <i>Haemophilus sp.</i>	Eradication	Cured
0557	6004	<i>Staphylococcus aureus</i>	Reduction	Cured
	6009	<i>Acinetobacter sp.</i>	Eradication	Cured
0635	1804	<i>Staphylococcus epidermidis</i>	Eradication	Better
	1810	<i>Haemophilus influenzae</i>	Eradication	Cured
	1811	<i>Staphylococcus aureus</i>	Eradication	Better
0798	0605	<i>Staphylococcus epidermidis</i>	Eradication	Better
0861	1715	<i>Haemophilus influenzae</i>	Eradication	Cured
	1717	<i>Haemophilus influenzae</i>	Eradication	Better
	1720	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	1725	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
	1727	<i>Haemophilus influenzae</i>	Eradication	Cured
	1730	<i>Staphylococcus aureus</i>	Eradication	Better

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
	1736	<i>Streptococcus sp.</i> <i>Klebsiella sp.</i>	Eradication	Better
	1737	<i>Staphylococcus aureus</i>	Eradication	Cured
0943	1308	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Reduction	Cured
	1320	<i>Staphylococcus epidermidis</i> <i>Klebsiella sp.</i>	Eradication	Cured
	1321	<i>Acinetobacter sp.</i>	Eradication	Cured
	1327	<i>Bacillus sp.</i>	Eradication	Cured
	1329	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1335	<i>Staphylococcus aureus</i> <i>Corynebacterium sp.</i>	Eradication	Better
	1337	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
	1343	<i>Staphylococcus aureus</i>	Persistence	Cured
0978	2119	<i>Streptococcus pyogenes</i>	Eradication	Cured
	2123	<i>Haemophilus influenzae</i>	Eradication	Cured
1001	2802	<i>Acinetobacter sp.</i>	Eradication	Cured
	2805	<i>Staphylococcus epidermidis</i>	Eradication	Better
	2815	<i>Coagulase-negative Staphylococcus sp.</i> <i>Streptococcus sp.</i>	Eradication	Better
	2823	<i>Moraxella catarrhalis</i> <i>Haemophilus influenzae</i>	Eradication	Cured
1008	1501	<i>Staphylococcus aureus</i>	Eradication	Cured
	1506	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	1508	<i>Acinetobacter sp.</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
1008	1509	<i>Staphylococcus aureus</i> <i>Proteus/Morganella sp.</i>	Eradication	Cured
	1512	<i>Streptococcus sp.</i> <i>Enterobacter sp.</i>	Eradication	Cured
	1516	<i>Staphylococcus aureus</i> <i>Acinetobacter sp.</i>	Eradication	Cured
	1533	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	1541	<i>Streptococcus pneumoniae</i>	Proliferation	Cured
	1544	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	2606	<i>Staphylococcus epidermidis</i> <i>Acinetobacter sp.</i>	Reduction	Cured
	2609	<i>Staphylococcus epidermidis</i> <i>Streptococcus sp.</i>	Eradication	Cured
	2614	<i>Staphylococcus epidermidis</i> <i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Better
	2619	<i>Coagulase-negative Staphylococcus sp.</i> <i>Haemophilus influenzae</i>	Eradication	Cured
	2620	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
	2623	<i>Staphylococcus aureus</i>	Eradication	Cured
	2638	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	2646	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
1025	0501	<i>Haemophilus influenzae</i>	Eradication	Better
1037	1101	<i>Streptococcus sp.</i>	Eradication	Better
	1106	<i>Staphylococcus aureus</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
1037	1115	<i>Staphylococcus epidermidis</i> <i>Coagulase-negative Staphylococcus sp.</i>	Reduction	Better
	1121	<i>Streptococcus sp.</i>	Eradication	Cured
	1127	<i>Micrococcus sp.</i>	Eradication	Cured
	1128	<i>Haemophilus influenzae</i>	Eradication	Cured
1046	1003	<i>Staphylococcus epidermidis</i>	Reduction	Cured
	1005	<i>Staphylococcus epidermidis</i>	Reduction	Better
	1009	<i>Staphylococcus aureus</i>	Eradication	Better
1052	2701	<i>Staphylococcus aureus</i>	Eradication	Better
1110	2301	<i>Staphylococcus aureus</i>	Eradication	Cured
	2302	<i>Coagulase-negative Staphylococcus sp.</i>	Eradication	Cured
	2305	<i>Haemophilus influenzae</i>	Eradication	Cured
	2307	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	2327	<i>Staphylococcus aureus</i>	Eradication	Cured
	2332	<i>Staphylococcus aureus</i>	Eradication	Cured
	2348	<i>Staphylococcus aureus</i>	Eradication	Cured
1112	1902	<i>Streptococcus pneumoniae</i>	Eradication	Better
1123	2405	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Eradication	Cured
1195	2902	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	2905	<i>Streptococcus pneumoniae</i>	Eradication	Cured
1196	3003	<i>Staphylococcus epidermidis</i>	Eradication	Cured

Continued

Inv. No.	Patient Number	Organism(s) Isolated	Microbiological Verdict	Physician Judgement
1229	3101	<i>Staphylococcus epidermidis</i>	Eradication	Better
	3104	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	3108	<i>Staphylococcus aureus</i>	Eradication	Cured
	3109	<i>Staphylococcus epidermidis</i> <i>Haemophilus influenzae</i>	Eradication	Cured
	3118	<i>Staphylococcus aureus</i>	Eradication	Unchanged
	3123	<i>Staphylococcus aureus</i>	Eradication	Cured
	3124	<i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>	Eradication	Cured
	3126	<i>Staphylococcus epidermidis</i>	Eradication	Cured
	3140	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	Reduction	Cured
1252	3402	<i>Staphylococcus aureus</i>	Eradication	Cured
	3405	<i>Streptococcus pneumoniae</i>	Eradication	Cured
	3413	<i>Acinetobacter sp.</i>	Persistence	Cured

Microbiological Efficacy

	TOTAL	ERADICATION		REDUCTION		PERSISTENCE		PROLIFERATION	
		N	%	N	%	N	%	N	%
TOBEX	91	63	69.2	16	17.6	8	8.8	4	4.4
Cipro	87	74	85.1	9	10.3	3	3.4	1	1.1

p=0.01, Cochran-Mantel-Haenszel rank score test

Reviewer's Comments: *Ciprofloxacin had a significantly ($p = 0.01$; Cochran-Mantel-Haenszel rank score test) higher percentage of culture-positive evaluative patients with eradication of conjunctival bacteria than did TOBEX.*

APPEARS THIS WAY
ON ORIGINAL

Clinical

A total of 178 culture-positive patients were included in the analysis of efficacy. The primary parameters in evaluating the clinical efficacy of ciprofloxacin versus tobramycin are the physician's judgment and clinical cardinal signs.

Physician Judgment for Culture-Positive Evaluative Patients

DAY	TOTAL	CURED		BETTER		UNCHANGED		WORSE		p-value*
		N	%	N	%	N	%	N	%	
3 TOBREX	42	3	7.1	35	83.3	3	7.1	1	2.4	0.80
Cipro	39	3	7.7	31	79.5	5	12.8	-	-	
7 TOBREX	91	62	68.1	22	24.2	6	6.6	1	1.1	0.23
Cipro	87	65	74.7	21	24.1	1	1.1	-	-	

* Cochran-Mantel-Haenszel rank score test

Reviewer's Comments: *No statistically significant treatment difference was found on Day 7 ($p = 0.23$).*

Physician Judgment for Intent-To-Treat Patients

DAY	TOTAL	CURED		BETTER		UNCHANGED		WORSE		p-value*
		N	%	N	%	N	%	N	%	
3 TOBREX	104	6	5.8	86	82.7	9	8.7	3	2.9	0.42
Cipro	104	7	6.7	79	76.0	14	13.5	4	3.8	
7 TOBREX	238	163	68.5	59	24.8	13	5.5	3	1.3	0.18
Cipro	227	167	73.6	52	22.9	4	1.8	4	1.8	

* Cochran-Mantel-Haenszel rank score test

Reviewer's Comments: *There was no significant difference ($p = 0.18$) on Day 7 between ciprofloxacin and tobramycin when all cases of acute conjunctivitis, regardless of microbiological results, were analyzed (i.e., intent-to-treat group).*

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The cardinal signs associated with conjunctivitis are exudation, erythema, discharge and palpebral and bulbar conjunctival inflammation.

Ciprofloxacin was not statistically different than tobramycin in reducing the severity of each of the clinical cardinal signs of conjunctivitis on days 3 and 7 ($p > 0.05$).

Resolution of Cardinal Signs for Culture-Positive Patients

DAY			BETTER		UNCHANGED		WORSE		p-value*
			N	%	N	%	N	%	
3	CONJ-B.	TOBREX	33	78.6	8	19.0	1	2.4	0.88
		Cipro	31	79.5	8	20.5	-	-	
	CONJ-P.	TOBREX	30	71.4	11	26.2	1	2.4	0.54
		Cipro	30	76.9	9	23.1	-	-	
	DISCHARGE	TOBREX	14	33.3	27	64.3	1	2.4	0.08
		Cipro	21	53.8	17	43.6	1	2.6	
	ERYTHEMA	TOBREX	13	31.0	28	66.7	1	2.4	0.12
		Cipro	19	48.7	19	48.7	1	2.6	
	EXUDATES	TOBREX	15	35.7	26	61.9	1	2.4	0.09
		Cipro	21	53.8	18	46.2	-	-	
7	CONJ-B.	TOBREX	83	91.2	7	7.7	1	1.1	0.56
		Cipro	77	88.5	9	10.3	1	1.1	
	CONJ-P.	TOBREX	82	90.1	8	8.8	1	1.1	0.94
		Cipro	78	89.7	9	10.3	-	-	
	DISCHARGE	TOBREX	49	53.8	40	44.0	2	2.2	0.17
		Cipro	55	63.2	32	36.8	-	-	
	ERYTHEMA	TOBREX	48	52.7	43	47.3	-	-	0.24
		Cipro	54	62.1	32	36.8	1	1.1	
	EXUDATES	TOBREX	60	65.9	31	34.1	-	-	0.92
		Cipro	58	66.7	29	33.3	-	-	

* Cochran-Mantel-Haenszel rank score test

Reviewer's Comments: *Ciprofloxacin was not statistically different than tobramycin in reducing the severity of each of the clinical cardinal signs of conjunctivitis on days 3 and 7 ($p > 0.05$)*

APPEARS THIS WAY
ON ORIGINAL

Resolution of Cardinal Signs for Intent-to-Treat Patients

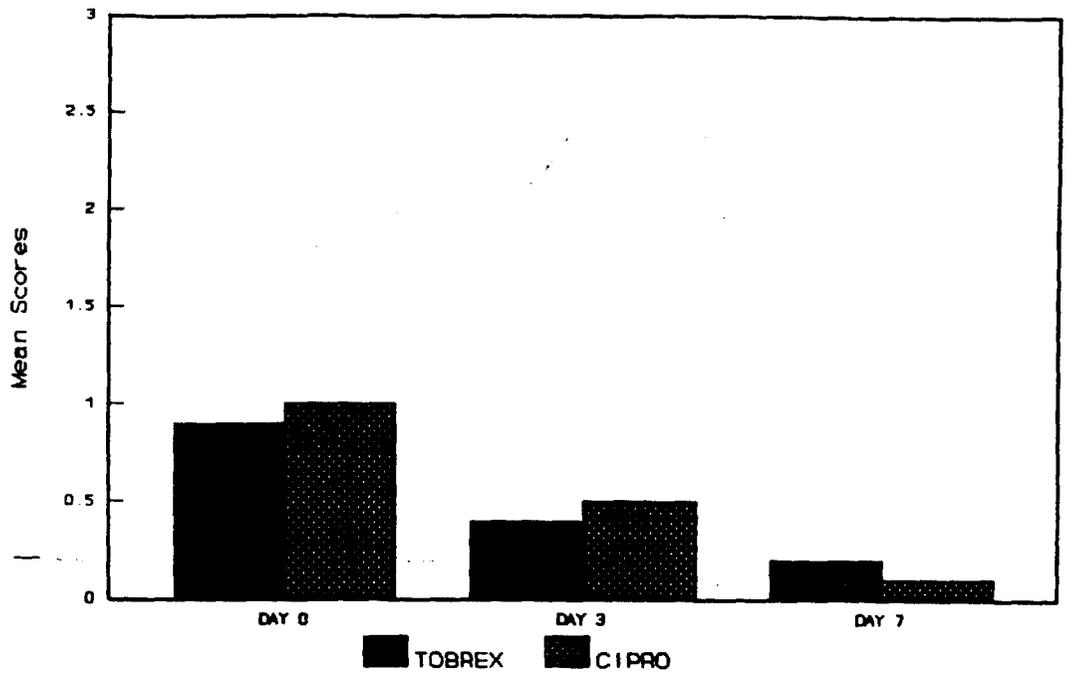
DAY			BETTER		UNCHANGED		WORSE		p-value*
			N	%	N	%	N	%	
3	CONJ-B.	TOBREX	80	76.9	22	21.2	2	1.9	0.175
		Cipro	72	68.6	30	28.6	3	2.9	
	CONJ-P.	TOBREX	75	72.1	26	25.0	3	2.9	0.435
		Cipro	70	66.7	33	31.4	2	1.9	
	DISCHARGE	TOBREX	43	41.3	60	57.7	1	1.0	0.784
		Cipro	42	40.0	61	58.1	2	1.9	
	ERYTHEMA	TOBREX	35	33.7	65	62.5	4	3.8	0.325
		Cipro	42	40.0	60	57.1	3	2.9	
	EXUDATES	TOBREX	47	45.2	56	53.8	1	1.0	0.988
		Cipro	47	44.8	58	55.2	-	-	
7	CONJ-B.	TOBREX	201	84.1	37	15.5	1	0.4	0.429
		Cipro	198	86.8	27	11.8	3	1.3	
	CONJ-P.	TOBREX	212	88.7	25	10.5	2	0.8	0.553
		Cipro	198	86.8	29	12.7	1	0.4	
	DISCHARGE	TOBREX	144	60.3	93	38.9	2	0.8	0.954
		Cipro	136	59.6	92	40.4	-	-	
	ERYTHEMA	TOBREX	124	51.9	112	46.9	3	1.3	0.421
		Cipro	126	55.3	101	44.3	1	0.4	
	EXUDATES	TOBREX	153	64.0	85	35.6	1	0.4	0.620
		Cipro	151	66.2	76	33.3	1	0.4	

* Cochran-Mantel-Haenszel rank score test

Reviewer's Comments: *Ciprofloxacin was not statistically different than tobramycin in reducing the severity of each of the clinical cardinal signs of conjunctivitis on days 3 and 7 ($p > 0.05$).*

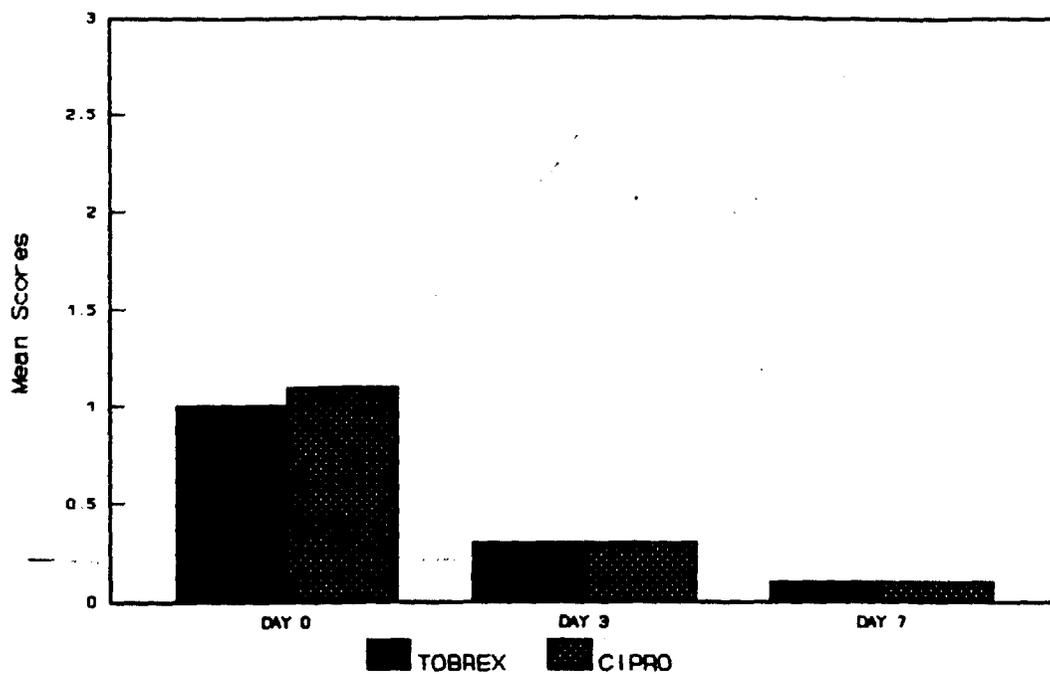
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Erythema

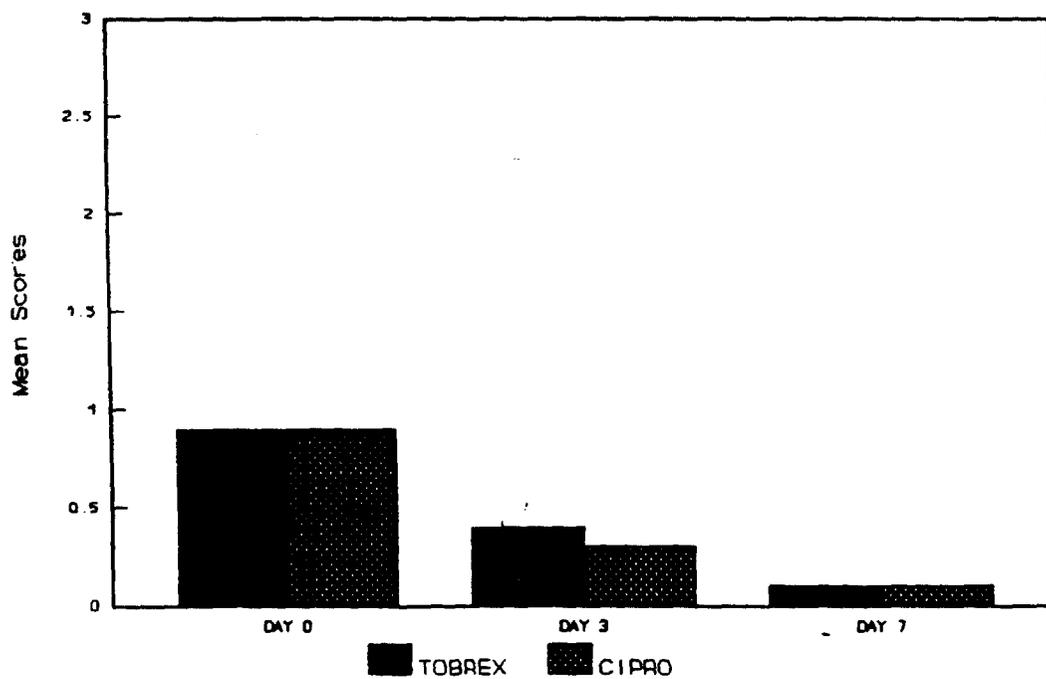


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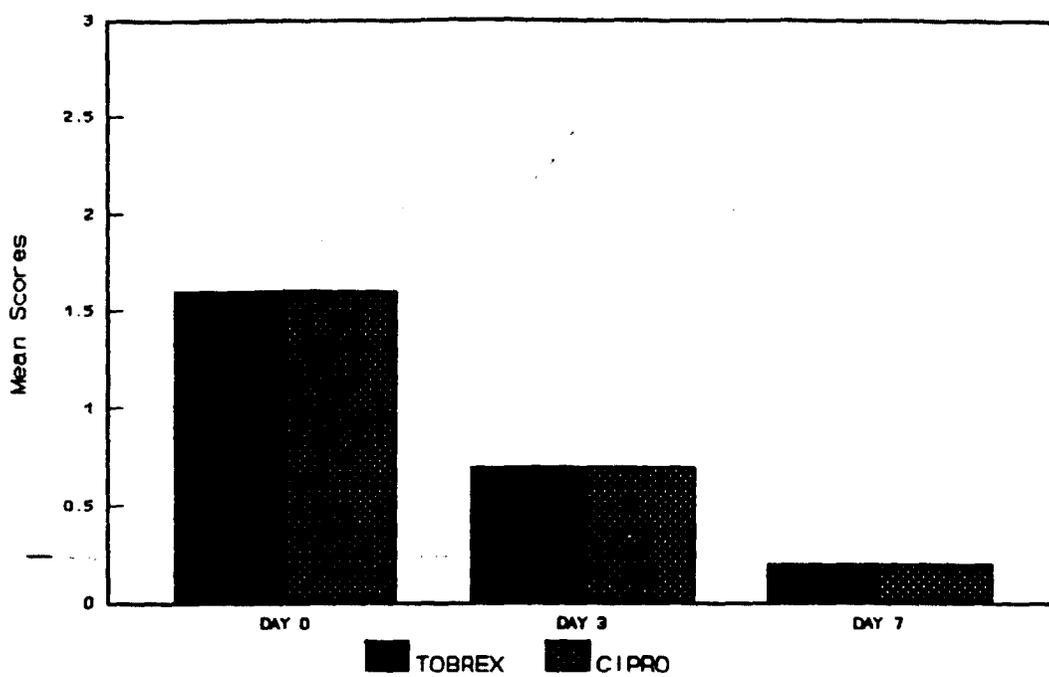
DISCHARGE



EXUDATES

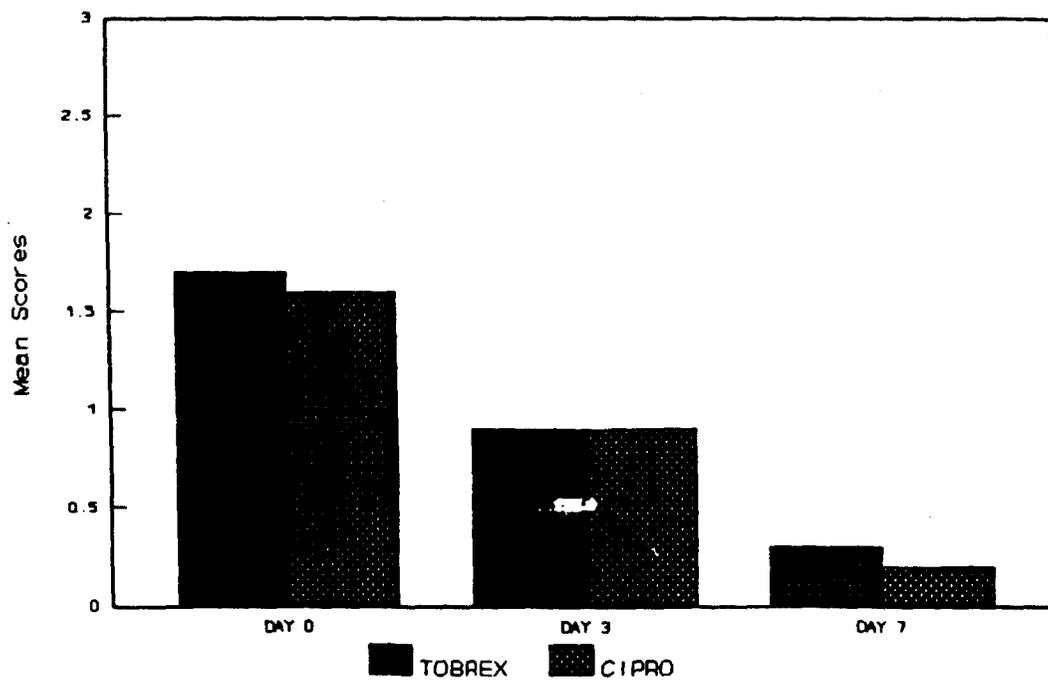


CONJ-P



9

CONJ-B



SAFETY

Ocular events related to Ciprofloxacin therapy were generally mild to moderate, nonserious and infrequent. Nonocular events related to Ciprofloxacin were not reported during the study. No serious events were reported, and none of the events resulted in ocular sequelae.

Ocular Events

Ocular events were generally mild to moderate, nonserious and infrequent. Nine patients using Ciprofloxacin experienced seventeen events, and eight patients using TOBREX experienced nine events. Ocular discomfort (1.2%), pruritus (1.2%) and hyperemia (1.2%) were the most frequent events associated with Ciprofloxacin, while ocular discomfort (0.8%) and blurred vision (0.8%) were the most frequent events associated with TOBREX. Other events associated with Ciprofloxacin included ocular pain, decreased visual acuity, corneal staining, dry eye, lid erythema, keratopathy, photophobia and tearing, which occurred at an incidence rate of 0.4%. Other events associated with TOBREX included conjunctivitis (in the untreated eye), keratitis, ocular discharge, ocular pruritus, pain, decreased visual acuity, corneal abrasion and stromal infiltrate, which occurred at an incidence rate of 0.4%.

Nonocular Events Related to Therapy

Nonocular events related to therapy were mild, nonserious and infrequent. Dermatitis and taste perversion (bad taste) were associated with TOBREX and resolved with discontinuation of therapy. Nonocular events related to Ciprofloxacin were not reported during the study.

Ocular Events Not Related to Therapy

Ocular events unrelated to therapy were generally mild to moderate, nonserious and infrequent. Subconjunctival hemorrhage (0.8%) was the most frequent event in patients treated with Ciprofloxacin, and hordeolum (0.8%) was the most frequent event in patients treated with TOBREX. Other events in patients treated with Ciprofloxacin included conjunctivitis (in the untreated eye), keratitis, chalazion, dacryocystitis and meibomitis, which occurred at an incidence rate of 0.4%. Other events in patients treated with TOBREX included conjunctivitis (in the untreated eye), keratitis, ocular discharge, conjunctival hemorrhage, keratoconjunctivitis and lid disorder, which occurred at an incidence rate of 0.4%.

Nonocular Events Not Related to Therapy

Nonocular events unrelated to therapy were generally mild to moderate, nonserious and infrequent. In the Ciprofloxacin-treated patients, allergy, pharyngitis, sinusitis and ear pain were reported at an incidence rate of 0.4%. In the TOBREX-treated patients, infection was reported at an incidence rate of 0.8%, and cellulitis, headache, dizziness, diarrhea, nausea and vomiting were reported at an incidence rate of 0.4%.

Serious Events

No serious events related or unrelated to therapy were reported during the study.

Frequency and Incidence of Medical Events

C-88-24

Coniunctivitis Indication

Coded Medical Events	Ciprofloxacin 0.3% Ophthalmic Ointment N = 244		Tobraymcin (TOBEX) 0.3% Ophthalmic Ointment N = 253	
	N	%	N	%
Ocular				
Discomfort	3	1.2	2	0.8
Pruritus	3	1.2	1	0.4
Hyperemia	3	1.2	0	
Pain	1	0.4	1	0.4
Decreased Visual Acuity	1	0.4	1	0.4
Corneal Staining	1	0.4	0	
Dry Eye	1	0.4	0	
Erythema Lid	1	0.4	0	
Keratopathy	1	0.4	0	
Photophobia	1	0.4	0	

Continued . . .

APPEARS THIS WAY
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Continued

Coded Medical Events	Ciprofloxacin 0.3% Ophthalmic Ointment N = 244		Tobramycin (TOBREX) 0.3% Ophthalmic Ointment N = 253	
Tearing	1	0.4	0	
Blurred Vision	0		2	0.8
Corneal Abrasion	0		1	0.4
Stromal Infiltrate	0		1	0.4
Subconjunctival Hemorrhage	2	0.8	0	
Conjunctivitis	1	0.4	1	0.4
Keratitis	1	0.4	0	
Chalazion	1	0.4	0	
Dacryocystitis	1	0.4	0	
Meibomitis	1	0.4	0	
Hordeolum	0		2	0.8
Discharge Eye NOS	0	1	0.4	
Conjunctival Hemorrhage	0		1	0.4
Keratoconjunctivitis	0		1	0.4
Lid Disorder	0		1	0.4
Nonocular				
Skin				
Dermatitis	0		1	0.4
Special Senses				
Taste Perversion	0		1	0.4

Continued . . .

Continued

Coded Medical Events	Ciprofloxacin 0.3% Ophthalmic Ointment N = 244		Tobraymcin (TOBEX) 0.3% Ophthalmic Ointment N = 253	
<u>Body as a Whole</u>				
Allergy	1	0.4	0	
Infection	0		2	0.8
Cellulitis	0		1	0.4
Headache	0		1	0.4
<u>Central Nervous System</u>				
Dizziness	0		1	0.4
<u>Digestive</u>				
Diarrhea	0		1	0.4
Nausea	0		1	0.4
Vomit	0		1	0.4
<u>Respiratory</u>				
Pharyngitis	1	0.4	0	
Sinusitis	1	0.4	0	
<u>Special Senses</u>				
Pain Ear	1	0.4	0	

Continued . . .

Reviewer's Comments: *There are no significant differences between Ciprofloxacin and Tobrex relative to the frequency and incidence of medical events. Judging from the fact that there were no reports of blurring (known to occur with ointments) it must be assumed that there was considerable under reporting of events.*

Discussion: This active controlled study demonstrated that Ciprofloxacin ophthalmic ointment had a significantly higher percentage of patients with eradication of conjunctival bacteria and showed no difference in the way it affects the resolution of this disease when compared to the active control. Statistically Ciprofloxacin Ointment was not worse than Tobrex both microbiologically and clinically and is as safe as Tobrex in the treatment of bacterial conjunctivitis.

It is noteworthy to comment on the significant difference of the cure rates on DAY 3 between the two conjunctivitis studies. In the placebo control study, 48% of the patients (14/29) were rated as cured, while in the active control study only 8% of the patients were rated as cured (3/39). The results of the placebo controlled study are not reproduced by the active control study.

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Corneal Ulcers

Protocol # C-95-85

Two studies were performed under this protocol

Study-1

A Clinical Evaluation of the Efficacy and Safety of Ciprofloxacin Ophthalmic Ointment 0.3% in Treating Bacterial Corneal Ulcers - Study 1

Ciprofloxacin Ophthalmic Ointment 0.3% has been evaluated for efficacy and safety in the treatment of corneal ulcers of bacterial etiology. Twenty-nine investigators participated in this open-label, multicenter and historically-controlled study. Ciprofloxacin's cure rate was compared to three control groups; a) that obtained historically with the solution dosage form, b) the historical "standard" therapy patient population to which the solution group was compared, and c) patients not eligible for ciprofloxacin treatment, but were treated with standard therapy.

A total of 166 patients diagnosed with presumed bacterial corneal ulcers were enrolled in the study and 166 were evaluative for safety since they were dosed at least one time with ciprofloxacin. A total of 106 patients were evaluative for efficacy. Patients were evaluative for efficacy provided: (1) their Day 0 corneal specimen was positive for bacteria only, (i.e., mixed bacterial-fungal cultures were not allowed), (2) no additional antibacterial or antifungal agent was used in conjunction with ciprofloxacin, (3) they dosed the drug according to the treatment regimen and (4) had a final follow-up physician evaluation following cessation of therapy.

Parameters used to measure and evaluate the clinical and microbiological efficacies of ciprofloxacin included physician judgment, ocular signs and symptoms and in vitro susceptibilities of the clinical isolates to ciprofloxacin wherever possible.

Physician impressions and evaluation of signs and symptoms were performed on treatment Day 0, Day 1, Day 3 (± 1 days), Day 7 (± 2 days) and on Day 14 (± 2 days). If dosing was continued past Day 16, a final evaluation was made when instillation of drug ceased. An evaluation was made at least one week off of therapy. Optional additional visits were allowed provided the investigator felt that the patient should be examined more frequently during the course of the study. Ocular signs and symptoms were not evaluated on such visits.

The scoring of ocular signs and symptoms (minimum, 0 = not present; maximum, 3 = severe) was reflective of the corneal ulcer, not of the transient symptomatology related to instillation of medication. Scoring standardization was obtained by referring to a Manual of Definitions which was contained in the Case Report Form. The following ocular symptoms were evaluated: discomfort, tearing, photophobia and itching. The ocular signs that were evaluated included: erythema, discharge, limbus, bulbar and palpebral conjunctiva, epithelial disease, focal stromal infiltrates, and aqueous reaction (flare and cells). Visual acuity of both eyes was determined at each required visit.

The physician evaluated the patient's overall clinical condition and made one of the following judgments regarding response to therapy at each follow-up visit: Cured (score 0) = absence of ocular signs and symptoms with complete reepithelialization of the cornea and apparent absence of infection; Improved (score 1) = a unit change in two or more ocular signs or symptoms with complete reepithelialization of the cornea and absence of apparent infection; Unchanged (score 2) = No change in ocular signs or symptoms; reepithelialization incomplete, with evidence of bacterial infection; Worse (score 3) = overall increase in ocular signs or symptoms; reepithelialization not progressing, evidence of bacterial infection.

The efficacy of Ciprofloxacin Ophthalmic Ointment 0.3% for treating bacterial corneal ulcers was determined by evaluating two parameters: (i) the physicians' clinical judgments and (ii) changes in ocular signs and symptoms. Available susceptibility results of the clinical isolates to ciprofloxacin was used to support clinical outcome.

Clinical success was achieved if the physician's clinical judgment at the final visit (last evaluation is off-therapy if available, otherwise the last on-therapy was used) was graded as cured or improved since, by definition, there is no indication of infection and complete reepithelialization has occurred in both of these categories. Bacteriological success was achieved when the offending microorganism isolated on Day 0 was susceptible in vitro to ciprofloxacin and/or there was no clinical evidence of bacterial infection.

APPEARS THIS WAY
ON ORIGINAL

LIST OF INVESTIGATORS

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
1053**	Penny A. Asbell, M.D. Mt. Sinai Medical Center New York, NY 10029-6574	09/03/91 - 08/10/92
511	James V. Aquavella, M.D. Genesee Valley Medical Center Rochester, NY 14618	07/09/91 - 10/22/92
1108	S. S. Badrinath, M.D. Medical Research Foundation Madras, India	01/28/91 - 01/24/92
362	Delmar R. Caldwell, M.D. Tulane University Medical Center New Orleans, LA 70112	12/18/90 - 05/14/92
1129	James L. Crabb, M.D. Eye Tech of Memphis Memphis, TN 38115	11/16/90 - 03/27/92
1337	Richard W. Darrell, M.D. Columbia - Presbyterian Medical Center New York, NY 10032	04/22/91 - 04/09/92
1363	Robert D. Deitch, M.D. Indiana University School of Medicine Indianapolis, IN 46202	07/22/91 - 03/19/92

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LIST OF INVESTIGATORS - Continued

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
1128	Richard A. Eiferman, M.D. Lions Eye Institute Louisville, KY 40202	02/12/91 - 03/31/92
1328	Robert S. Feder, M.D. Northwestern University Chicago, IL 60601	07/22/91 - 03/17/92
1325**	Larry A. Fish, M.D. Central Medical Center Pittsburg, PA 15219	04/22/91 - 04/24/92
1334	Jonathan M. Frantz, M.D. Eye Center of Florida Ft. Myers, FL 33901	06/03/91 - 02/22/92
372	Robert A. Hyndiuk, M.D. Eye Institute Milwaukee, WI 53226	04/05/91 - 03/18/92
557	Michael S. Insler, M.D. LSU Eye Center New Orleans, LA 70112	12/20/91 - 05/15/92
845	Harold R. Katz, M.D. The Krieger Eye Institute Baltimore, MD 21215-5271	02/12/91 - 03/23/92
1019	Bruce H. Koffler, M.D. 120 N. Eagle Creek Drive, Suite 431 Lexington, KY 40509	11/15/90 - 04/14/92

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LIST OF INVESTIGATORS - Continued

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
987	Frances D. McMullan, M.D. Atlanta Eye Surgery Group Atlanta, GA 30327	06/03/91 - *
1387**	Sheldon M. Oberfeld, M.D. 29001 Cedar Road, Suite 670 Lyndhurst, OH 44124	09/04/91 - 05/19/92
1322	Eric S. Pearlstein, M.D. Ophthalmology Associates of Bay Ridge Brooklyn, NY 11209	04/22/91 - 04/18/92
628	John W. Reed, M.D. Bowman Gray School of Medicine Winston-Salem, NC 27103	07/10/91 - 04/01/92
1327**	James J. Reidy, M.D. SUNY - Department of Ophthalmology Buffalo, NY	09/19/91 - 04/24/92
1049	Steven I. Rosenfeld, M.D. Delray Eye Associates Delray Beach, FL 33484	04/10/91 - 02/27/92
1064	George O. D. Rosenwasser, M.D. Pennsylvania State University Hershey, PA 47033	02/21/91 - 03/25/92
1283	Eric J. Rothchild, M.D. 16244 S. Military Trail, Suite 690 Delray Beach, FL 33484	02/01/91 - 02/28/92

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LIST OF INVESTIGATORS - Continued

<u>Inv. No.</u>	<u>Name/Address</u>	<u>Dates of Participation</u>
1323	Samuel M. Salamon, M.D. Cataract Eye Center of Cleveland Cleveland, OH 44115	04/22/91 - 04/30/92
1329	Richard J. Selsø, M.D. Ochsner Clinic-Dept. of Ophth. New Orleans, LA 70121	07/15/91 - 05/12/92
1340	Joseph W. Spadafora, D.O. Community Eye Center Port Charlotte, FL 33952	06/21/91 - 02/26/92
1424	Daniel W. Steen, M.D. Henry Ford Hosp. - Dept. of Ophthalmology 2799 W. Grand Blvd. Detroit, MI 48202	08/26/91 - *
861	Saul Ullman, M.D. Medical Center Clinic Pensacola, FL 32514	04/30/91 - 02/24/92
1292	Michael P. Vrabec, M.D. University of Vermont Medical School Burlington, FL 32514	05/29/91 - 04/07/92

These investigators were geographically located east of the Mississippi River.
Dr. Badrinath of India was placed in this group at random.

*For this submission, 12/2/91 was the cutoff date.

**These four investigators did not contribute any patients.

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RESULTS**Patient Population****Patient Evaluability**

Enrollment and evaluability status for all patients by investigator are summarized in the following table.

Distribution of Evaluative Patients
Study 1

INV	Evaluative	
	No	Yes
362	6	14
372	4	16
557	2	-
628	2	1
845	8	5
861	1	2
987	2	-
1019	4	2
1049	3	3
1108	4	19
1128	7	15
1164	2	11
1129	2	1
1283	2	1

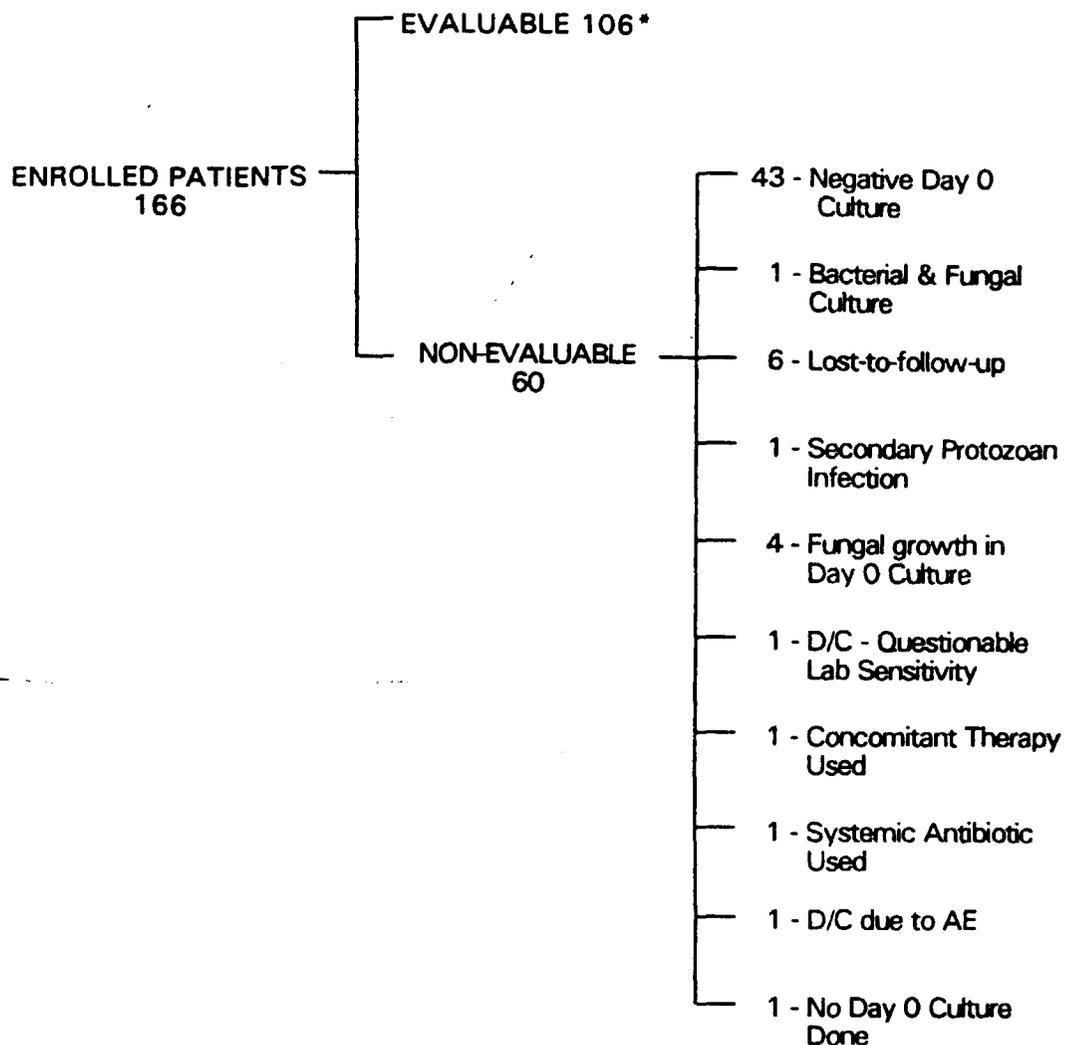
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Table - Continued

INV	Evaluative	
	No	Yes
1292	1	2
1322	3	1
1323	1	-
1328	-	4
1329	1	-
1334	1	-
1337	3	5
1340	-	1
1363	-	2
1424	-	1
Total	60	106

Of the 166 patients enrolled in the study, 166 were evaluative for safety and 106 (64%) were evaluative for efficacy. Sixty (36%) patients were nonevaluative. Of this number, 43 were culture negative upon enrollment and the remaining 17 were excluded for reasons listed in the table. The following diagram shows the distribution of all enrolled patients.

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Reviewer's Comments: *If therapy was started after Day 1, patients who used concomitant therapy and systemic antibiotics after day 1 should have been evaluable and considered failures. The same applies to patients lost to follow up and patients with adverse reactions.*

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Discontinued Patients:**Study 1**

Inv. Number	Patient Number	Reason for Discontinuance	Treatment	Days on Treatment
1108	1015*	Treatment Failure	Ciprofloxacin	5
1322	3804	Treatment Failure	Ciprofloxacin	10
1328	5504	Treatment Failure	Ciprofloxacin	3
1128	1511*	Treatment Failure/ Adverse Medical Event	Ciprofloxacin	6
372	619	Adverse Medical Event	Ciprofloxacin	1
1128	1518	Worsening of symptoms and physical findings (culture-negative)	Ciprofloxacin	1
557	101	Culture - Negative	Ciprofloxacin	7
362	716	Culture-Negative	Ciprofloxacin	4
845	901	Culture - Negative	Ciprofloxacin	7
	903	Culture - Negative	Ciprofloxacin	8
	907	Culture - Negative	Ciprofloxacin	3
	911	Culture - Negative	Ciprofloxacin	14
	1229	2601	Culture - Negative	Ciprofloxacin
1322	2603	Culture - Negative	Ciprofloxacin	6
	3801	Culture - Negative	Ciprofloxacin	6
845	910	Lost to follow-up	Ciprofloxacin	4
1128	1504	Lost to follow-up	Ciprofloxacin	2
	1510	Lost to follow-up	Ciprofloxacin	2
1337	2704	Lost to follow-up	Ciprofloxacin	6
557	102**	In vitro susceptibility test results	Ciprofloxacin	5

*Treatment failure on Ciprofloxacin Ophthalmic Ointment 0.3%

**Patient improved, but discontinued based upon laboratory susceptibility results unobtainable by Alcon.

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The seven culture-positive patients that were evaluated as unchanged or worse, and required a change in therapy, were defined as treatment failures. This information is summarized in the following table:

Patient No.	Organism(s) Isolated	Susceptibility to Ciprofloxacin	Comments	Discontinued
911	Coag. Neg. Staph.	?	Unchanged	No
1012	<i>S. aureus</i>	Yes	Worse; Panophthalmitis, eye enucleated	Yes
1015	<i>P. aeruginosa</i>	Yes	Worse; eye enucleated	Yes
	<i>C. equi</i>	Yes		
	<i>S. epidermidis</i>	Yes		
1511	<i>S. aureus</i>	Yes	Unchanged; Patient had emergency corneal transplant	Yes
1916	<i>S. pneumoniae</i>	Yes	Unchanged	No
3804	<i>S. epidermidis</i>	Yes	Unchanged	Yes
5504	<i>S. pneumoniae</i>	?	Unchanged	Yes

? = Definitive end-point not determined.

Cultures from most of these seven patients yielded bacteria (including a methicillin-resistant *S. epidermidis* strain) that were shown to be susceptible *in vitro* to $\leq 1.0 \mu\text{g/mL}$ ciprofloxacin: Patient 911 (Unchanged) - coagulase-negative *Staphylococcus* resistant to $\geq 2.0 \mu\text{g/mL}$; Patient 1012 (Worse) - *Staphylococcus aureus*; Patient 1015 (Worse) - *Pseudomonas aeruginosa*; *Corynebacterium equi* and *Staphylococcus epidermidis* (MRSE); Patient 1511 (Unchanged) - *Staphylococcus aureus*; Patient 1916 (Unchanged) - *Streptococcus pneumoniae*; Patient 3804 (Worse) - *Staphylococcus epidermidis*; Patient 5504 (Unchanged) - *Streptococcus pneumoniae* (MIC underdetermined); Patient 102 had a strain of a viridans group *Streptococcus* isolated from his ulcer and was improved after 5 days of ciprofloxacin therapy. However, the investigator discontinued this patient stating that the bacterial strain isolated was resistant to $> 2.0 \mu\text{g/mL}$ ciprofloxacin. No further results were available, and by standard definition this organism's resistance to ciprofloxacin cannot be determined (i.e., $\geq 4.0 \mu\text{g/mL}$). This patient was not evaluated as a treatment failure to ciprofloxacin, since he was improved at the time of discontinuation.

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Demographics

Demographics for patients evaluative for efficacy are outlined in the following tables.

STUDY	AGE			
	N	MEAN	STD	RANGE
1	105	51.1	22.94	3-94

STUDY	TOTAL N	SEX			
		MALE		FEMALE	
		N	%	N	%
1	106	57	53.8	49	46.2

STUDY	TOTAL N	RACE							
		CAUCASIAN		BLACK		ASIAN		OTHER	
		N	%	N	%	N	%	N	%
1	106	57	53.8	23	21.7	-	-	26	24.5

STUDY	TOTAL N	AFFECTED EYE			
		OD		OS	
		N	%	N	%
1	106	55	51.9	51	48.1

STUDY	TOTAL N	DAY 0 ULCER DEPTH					
		Superficial		Mid-Stromal		Deep Stromal	
		N	%	N	%	N	%
1	106	49	46.2	38	35.8	19	17.9

	DAY 0 ULCER DEPTH						
	TOTAL	Superficial		Mid-Stromal		Deep Stromal	
STUDY	N	N	%	N	%	N	%
1	106	34	32.1	50	47.2	22	20.8

STUDY	DURATION (Days)			
	N	MEAN	STD	RANGE
1	106	6.9	9.54	

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EfficacyMicrobiology

The culture-positive frequency of Day 0 bacterial corneal scrapings in all 166 enrolled patients was 73% (121/166), with individual investigators exhibiting frequencies of 0% to 100%. Of the 121 culture-positive patients, 106 (64%) were evaluative for efficacy. Sixty patients of the 166 patients enrolled did not meet all of the evaluability criteria; 43 were culture-negative on entry into the study on Day 0 and 17 failed to meet other protocol criteria.

The frequencies of bacterial groups isolated from the corneal ulcers of patients that were culture-positive and evaluative for efficacy are presented in the following table.

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**Frequency of Day 0 Infective Bacteria
in Patients Evaluative for Efficacy**

Study 1

Bacteria	No. of Isolates	% of Isolates
Gram-Positives:		
<i>Staphylococcus aureus</i>	26	18.8
<i>Staphylococcus epidermidis</i>	28	20.3
<i>Staphylococcus warneri</i>	4	2.9
<i>Staphylococcus haemolyticus</i>	3	2.2
<i>Staphylococcus Coag.-Neg. (nonspeciared)</i>	8	5.8
<i>Stomatococcus spp.</i>	1	0.7
<i>Streptococcus pneumoniae</i>	6	4.3
<i>Streptococcus Grp. G</i>	1	0.7
Streptococcus Viridans Grp.:		
<i>Streptococcus sanguis</i>	3	2.2
nonspeciared	2	1.4
<i>Streptococcus equisimilis</i>	1	0.7
<i>Streptococcus spp.</i>	1	0.7
<i>Corynebacterium equi</i>	2	1.4
<i>Corynebacterium pseudodiphtheriticum</i>	1	0.7
<i>Corynebacterium spp.</i>	13	9.4
<i>Aerococcus spp.</i>	1	0.7
<i>Actinobacillus spp.</i>	1	0.7
<i>Bacillus spp.</i>	1	0.7
<i>Gram-positive bacillus, no ID</i>	1	0.7
<i>Propionibacterium acnes</i>	2	1.4
<i>Peptostreptococcus spp.</i>	1	0.7
<i>Clostridium perfringens</i>	1	0.7
Anaerobes, no ID	1	0.7
GRAM-POSITIVE SUBTOTALS n (%)	109	79.0
Gram-Negatives:		
<i>Pseudomonas aeruginosa</i>	11	8.0
<i>Serratia marcescens</i>	4	2.9
<i>Klebsiella oxytoca</i>	3	2.2
<i>Enterobacter aerogenes</i>	1	0.7
<i>Pasteurella multocida</i>	1	0.7
<i>Morganella morganii</i>	1	0.7
<i>Achromobacter spp.</i>	1	0.7
<i>Haemophilus influenzae</i>	1	0.7

Bacteria	No. of Isolates	% of Isolates
<i>Haemophilus spp.</i>	1	0.7
<i>Moraxella (B.) catarrhalis</i>	2	1.4
<i>Moraxella nonliquefaciens</i>	1	0.7
<i>Moraxella lacunata</i>	1	0.7
<i>Moraxella spp. (nonspeciared)</i>	1	0.7
GRAM-NEGATIVE SUBTOTALS n (%)	29	21.0
GRAND TOTALS	138	100

Clinical

These results are summarized in the following tables:

STUDY	TOTAL	SUMMARY OF FINAL PHYSICIAN JUDGMENT							
		CURED		IMPROVED		UNCHANGED		WORSE	
		N	%	N	%	N	%	N	%
1	106	94	88.7	5	4.7	4	3.8	3	2.8

STUDY	TOTAL	SUMMARY OF FINAL PHYSICIAN IMPRESSION							
		CURED		IMPROVED		UNCHANGED		WORSE	
		N	%	N	%	N	%	N	%
Ulcer Diam	< 2 mm	N	%	N	%	N	%	N	%
1	34	33	97.1	1	2.9	-	-	-	-
Ulcer Diam	2 - 4 mm	N	%	N	%	N	%	N	%
1	50	46	92.0	1	2.0	2	4.0	1	2.0
Ulcer Diam	> 4 mm	N	%	N	%	N	%	N	%
1	22	15	78.9	3	13.6	2	9.1	2	9.1
Superficial									
1	49	46	93.9	2	4.1	-	-	1	2.0
Mid-Stromal									
1	38	33	86.9	2	5.3	2	5.3	1	2.6
Deep Stromal									
1	19	15	78.9	1	5.3	1	5.3	2	10.5

Cumulative Efficacy Results

	Cured		Improved		Unchanged		Worse	
Treatment Phase	88	(83.0%)	11	(10.4%)	4*	(3.8%)	3*	(2.8%)
Off-Therapy**	87	(98.9%)	1	(1.1%)	-	-	-	-
Final Evaluation	94	(88.7%)	5	(4.7%)	4*	(3.8%)	3*	(2.8%)

*These patients are treatment failures.

**Eighteen patients did not have an off-therapy evaluation.

This table allows the determination of (1) overall clinical efficacy at the end of the treatment phase (Day 14 or > Day 16), (2) clinical efficacy after treatment had been stopped for at least one week (off-therapy) and (3) a final evaluation, either off-therapy or if this was not available, the last treatment day. 99 patients (93.4%) benefitted from treatment with ciprofloxacin (Cured or Improved) at the final evaluation. The off-therapy evaluation was to determine whether patients who were cured or improved (i.e., healed) did not regress after therapy was discontinued and, equally importantly, whether the ulcer further improved in those patients that were not cured. The results demonstrate that patients did not regress but continued to improve. The ulcers resolved (cured or improved) in all of the 88 patients that had off-therapy evaluations.

Forty-three patients diagnosed with bacterial corneal ulcers were culture-negative, but were treated with ciprofloxacin ointment. Of this group, 36 completed therapy and 34 (94.4%) were judged as clinical successes.

Physician Impression by Ulcer Size

Study 1

	Cured		Improved		Unchanged		Worse	
	N	(%)	N	(%)	N	(%)	N	(%)
DAY 0 ULCER DIAM. (mm)								
< 2 mm	33	(97.1)	1	(2.9)	-	-	-	-
2-4 mm	46	(92.0)	1	(2.0)	2	(4.0)	1	(2.0)
> 4 mm	15	(68.2)	3	(13.6)	2	(9.1)	2	(9.1)
All Ulcers (Diam.)	94	(88.7)	5	(4.7)	4	(3.8)	3	(2.8)
DAY 0: STROMAL DEPTH								
Superficial	46	(93.9)	2	(4.1)	-	-	1	(2.0)
Mid-Stromal	33	(86.8)	2	(5.3)	2	(5.3)	1	(2.6)
Deep Stromal	15	(78.9)	1	(5.3)	1	(5.3)	2	(10.5)
All Ulcers (Depth)	94	(88.7)	5	(4.7)	3	(2.8)	4	(1.9)

In the above table, the clinical effectiveness of treatment with ciprofloxacin in relation to ulcer diameter and stromal depth is presented. Ulcers < 2 mm and 2-4 mm in diameter had a better clinical success rate (100%, 94%, respectively) than > 4 mm (81.8%) ulcers. Superficial and mid-stromal ulcers have a likelihood of resolving, with 98% and 92.1% success rates respectively, as compared to deep-stromal ulcers (84.2%).

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Safety

Ciprofloxacin Ophthalmic Ointment 0.3% was evaluated for safety in 166 patients with bacterial corneal ulcers. Adverse events related to ciprofloxacin were generally mild, nonserious and did not interrupt continuation in the study. No serious events related to ciprofloxacin were reported, and no patient was discontinued from the study due to a serious treatment-related event.

Demographics

Demographics for all patients with and without adverse events were analyzed for trends in age, sex and race. Forty of the 166 patients (24.1%) receiving Ciprofloxacin Ophthalmic Ointment 0.3% experienced adverse events. No difference between the patient population demographics with or without adverse events was observed.

Concomitant Medications

Ancillary drugs which were available for use at Study Investigator's discretion included topical ophthalmic cyclopentolate 1.0%, atropine 1.0%, phenylephrine 2.5% and proparacaine 0.5%. None of the events were associated with the combination of study and nonstudy drugs, and no drug interactions were noted.

Ocular Events

Ocular events related to Ciprofloxacin Ophthalmic Ointment 0.3% were generally mild, nonserious and did not interrupt continuation in the study. Twenty-seven patients experienced thirty events related to ciprofloxacin. The most frequently noted ocular event associated with ciprofloxacin was a white crystalline precipitate in the superficial portion of the corneal defect which was seen in twenty-one patients (12.7%). The precipitate was unrelated to age or sex of patients, organism cultured, stromal depth or size of ulcer; neither was any association seen between size of ulcer, depth of involvement and days to resolution. Nine of the precipitates were described as white; ten were characterized as crystalline precipitates, and eleven were noted in the zone of defect. While the exact etiology of the appearance of the precipitate is unknown, it has been hypothesized that the difference between tearfilm and quinoline pH may be a factor in its appearance and/or there may be an electrochemical event occurring in the denuded epithelium due to the difference in epithelial cell and quinoline charge. In the 21 patients noted with the event, the onset of the precipitate was within 24 hours to 13 days after starting therapy. In one of the 21 patients, the precipitate was immediately scraped clear. In four patients, resolution of the precipitate occurred within the first 24 to 96 hours without treatment. In seven patients, resolution was noted in 6 to 14 days. In eight patients, exact resolution days were unavailable upon exiting the study, as small amounts of precipitate were visible; follow-up examinations (16 to 35 days after onset) revealed the precipitates had completely resolved. In the remaining one patient, outcome information was unavailable (patient was lost to follow-up). The precipitate did not interrupt continued use of ciprofloxacin, and eighteen of the twenty-one patients completed the study as planned (two patients were lost to follow-up, one patient was a treatment failure). Except for scraping of the precipitate in one patient, no adjunctive treatment was required, and the precipitate was considered nonserious by the Study Investigator and Medical Monitor. Other events related to ciprofloxacin included discomfort characterized by burning (3.0%), blurred vision (1.2%), new corneal lesions (0.6%) and tearing (0.6%).

Nonocular

Nonocular events were mild, infrequent, nonserious and did not interrupt continuation in the study. Three patients noted taste perversion (metallic, bitter taste) (1.8%) and nausea (0.6%) following ciprofloxacin instillation, which resolved without treatment.

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