Frequency and Incidence of Adverse Events

Study 1

| Adverse Events | Ciprofloxacin Ophthalmic Ointment 0.3% N = 166 | |
|---|---|---|
| | N | % |
| **Ocular** | | |
| White Precipitate | 21 | 12.7 |
| Discomfort | 5 | 3.0 |
| Blurred Vision | 2 | 1.2 |
| Corneal Lesion | 1 | 0.6 |
| Tearing | 1 | 0.6 |
| Glaucoma | 1 | 0.6 |
| Perforated Corneal Ulcer | 1 | 0.6 |
| Corneal Edema | 1 | 0.6 |
| Increased Intraocular Pressure | 1 | 0.6 |
| Surgical/Medical/Procedure | 1 | 0.6 |
| Pupillary Block/Iridectomy | 1 | 0.6 |
| Endophthalmitis | 1 | 0.6 |
| Panophthalmitis | 1 | 0.6 |
| | | |
| **Nonocular** | | |
| Digestive<br>Nausea | 2 | 1.2 |
| Special Senses<br>Taste Perversion | 3 | 1.8 |
| Skin<br>Contact Dermatitis | 2 | 1.2 |

Serious Events Reported

Five serious events (perforated corneal ulcer, surgical/medical procedure, pupillary block/iridectomy, endophthalmitis, panophthalmitis) secondary to the corneal ulcer itself or an ocular injury were reported.

Discussion:

Safety:
These data demonstrate Ciprofloxacin Ophthalmic Ointment 0.3% lacked ophthalmic and systemic toxicity and was reasonably well tolerated by patients with bacterial corneal ulcers.

**Study #2**

RESULTS

Patient Population

1. - Patient Evaluability

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

Study 2

| | Evaluative | |
|---|---|---|
| Investigator | No | Yes |
| 314 | 1 | - |
| 354 | 2 | 6 |
| 498 | 6 | 4 |
| 574 | 2 | 3 |
| 635 | 6 | 3 |
| 798 | 1 | - |
| 1001 | 5 | - |
| 1007 | 4 | 1 |
| 1010 | 1 | - |
| 1027 | 3 | 3 |
| 1117 | - | 4 |
| 1119 | 1 | 1 |
| 1123 | 6 | 8 |
| 1148 | 3 | - |
| 1310 | 1 | - |
| 1355 | 1 | 3 |
| 1388 | 3 | 1 |
| 1427 | 3 | 2 |
| Total | 49 | 39 |

LIST OF INVESTIGATORS - Continued

| Inv. No. | Name/Address | Dates of Participation* |
|---|---|---|
| 1123 | Michael B. Limberg, M.D.<br>1457 Marsh St., Suite 100<br>San Luis Obispo, CA 93401 | 11/21/90 - * |
| 1119 | David L. McCartney, M.D.<br>Texas Tech University Health Science Center<br>Lubbock, TX 79430 | 01/29/91 - 02/12/92 |
| 498 | James P. McCulley, M.D.<br>University of Texas Health Science Center<br>Dallas, TX 75235 | 01/16/91 - * |
| 1355 | Robert R. McCulloch, M.D.<br>Samaritan's Physician Center<br>Phoenix, AZ 85006 | 05/16/91 - 02/13/92 |
| 1027 | Rex L. Repass, M.D.<br>Eye Care Austin<br>Austin, TX 78704 | 01/31/91 - 01/20/92 |
| 354 | J. James Rowsey, M.D.<br>Dean A. McGee Eye Institute<br>Oklahoma City, OK 73104 | 01/29/91 - 10/02/91 |
| 635 | David J. Schanzlin, M.D.<br>Bethesda Eye Institute<br>St. Louis, MO 63110 | 05/29/91 - 03/06/92 |
| 1110** | Neal A. Sher, M.D.<br>9th and Nicollet<br>Minneapolis, MN 55402 | 10/24/90 - 04/07/92 |
| 1333** | Eliot B. Siegel, M.D.<br>HCMG - Balboa Medical Group<br>Northridge, CA 91324 | 06/11/91 - * |

APPEARS THIS WAY
ON ORIGINAL

**LIST OF INVESTIGATORS - Continued**

| Inv. No. | Name/Address | Dates of Participation* |
|---|---|---|
| 1010 | Mark A. Terry, M.D.<br>Devers Eye Institute<br>Portland, OR 97210 | 06/11/91 - * |
| 318 | David W. Vastine, M.D.<br>491 30th St.<br>Oakland, CA 94609 | 08/07/91 - 04/24/92 |
| 1007 | Thomas R. Walters, M.D.<br>Eye Care Austin<br>Austin, TX 78704 | 12/19/91 - * |
| 574 | Kirk R. Wilhelmus, M.D.<br>Cullen Eye Institute<br>Houston, TX 77030 | 01/16/91 - 02/18/92 |
| 1001 | A. Thomas Williams, M.D.<br>The Rocky Mountain Eye Center<br>Salt Lake City, UT 84107 | 05/15/91 - 03/10/92 |
| 1427 | Thomas C. Wolf, M.D.<br>Dean A. McGee Eye Institute<br>Oklahoma City, OK 73104 | 10/09/91 - * |
| 798 | Richard W. Yee, M.D.<br>University of Texas Health Science Center<br>San Antonio, TX 78284-7779 | 09/18/91 - 02/19/92 |
| 1117 | Ralph W. Zabel, M.D.<br>General Hospital<br>Ottawa, Ontario | 10/22/91 - 11/23/92 |

---

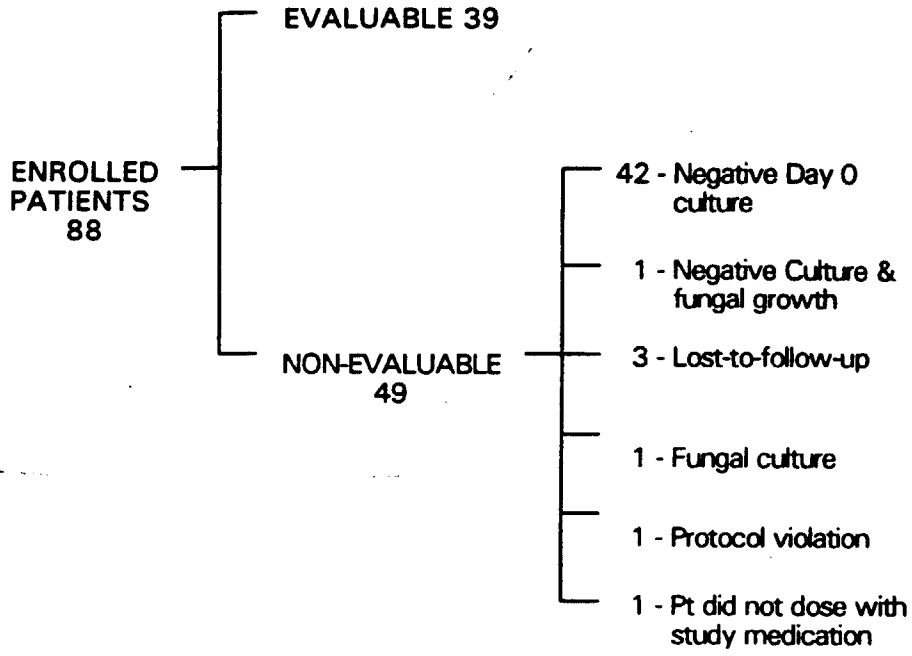
These investigators were geographically located west of the Mississippi River.

*For this submission, 08/19/92 was the cut-off date. The study is ongoing at these sites.

**These six investigators did not enroll any patients.

APPEARS THIS WAY
ON ORIGINAL

Of the 88 patients enrolled in the study, 87 were evaluative for safety (one patient not dosed) and 39 (45%) were evaluative for efficacy. Forty-nine (56%) patients were nonevaluative. Of this number, 42 were culture negative upon enrollment and the remaining 7 were excluded for reasons listed in the table. The following diagram shows the distribution of all enrolled patients.




**Reviewer's Comments:** *The 3 patients lost to follow up should have been considered treatment failures.*

The 11 patients that were discontinued are listed in the table below. Three patients (1606, 1707, 6104) were discontinued from the study prior to 14 (± 2) days of treatment and were considered treatment failures. Four patients (2803, 3502, 6104, 6204) were discontinued due to medical events. The remaining four patients were discontinued for the following reasons: culture-negative (2); lost to follow-up (1); protocol violation (1).

Discontinued Patients

Study 2

| Inv. Number | Patient Number | Reason for Discontinuance | Treatment | Days on Treatment |
|---|---|---|---|---|
| 498 | 1606 | Treatment Failure | Ciprofloxacin | 14 |
| 1123 | 1707 | Treatment Failure | Ciprofloxacin | 6 |
| 1427 | 6104 | Treatment Failure | Ciprofloxacin | 4 |
| 1027 | 2803 | Adverse Medical Event Culture-negative | Ciprofloxacin | 7 |
| 1001 | 3502 | Adverse Medical Event Culture-negative | Ciprofloxacin | 19 |
| 1427 | 6104 | Adverse Medical Event | Ciprofloxacin | 2 |
| 1007 | 6204 | Adverse Medical Event Culture-negative | Ciprofloxacin | 7 |
| 498 | 1604 | Culture-negative | Ciprofloxacin | 8 |
| 1001 | 3503 | Culture-negative | Ciprofloxacin | 8 |
| 354 | 301 | Lost to Follow-up | Ciprofloxacin | 6 |
| 314 | 4201 | Protocol Violation | Ciprofloxacin | 3 |

Culture-positive patients that were evaluated as unchanged or worse, and required a change in therapy, were defined as treatment failures. This information, summarized in the following table, shows that the ulcers of three patients on this study failed to respond to Ciprofloxacin Ophthalmic Ointment 0.3% therapy. The strain of S. aureus isolated from Patient 1606 was not tested in-house for resistance to ciprofloxacin. The physician assessed this patient as worse and discontinued him from the study. Patient 1707 was worse and discontinued, but the strain of S. epidermidis isolated from this patient's eye was susceptible to < 3.0 μg/mL ciprofloxacin.

| Patient No. | Organism(s) Isolated | Susceptibile to ≤ 3.0 μg/mL Ciprofloxacin | Comments | Discontinued |
|---|---|---|---|---|
| 1606 | *S. aureus* | N.D.* | Worse; put on other therapy | Yes |
| 1707 | *S. epidermidis* | Yes | Patient worse at Day 7, put on other therapy | Yes |
| 6104 | *S. epidermidis* | Yes | Unchanged; Perforated | Yes |

*Not Determined

Demographics

| Age | | | | |
|---|---|---|---|---|
| Study | N | Mean | STD | Range |
| 2 | 39 | 44.5 | 23.06 | 13-92 |

| Sex | | | | | |
|---|---|---|---|---|---|
| Study | N | N | % | N | % |
| 2 | 39 | 19 | 48.7 | 20 | 51.3 |

| Race | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Caucasian | | Black | | Asian | | Other | |
| Study | N | N | % | N | % | N | % | N | % |
| 2 | 39 | 32 | 82.1 | 1 | 2.6 | 1 | 2.6 | 5 | 12.8 |

| Affected Eye | | | | | |
|---|---|---|---|---|---|
| | Total | OD | | OS | |
| Study | N | N | % | N | % |
| 2 | 39 | 18 | 46.2 | 21 | 53.8 |

| Day 0 Ulcer Depth | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Total | Superficial | | Mid-Stromal | | Deep Stromal | |
| Study | N | N | % | N | % | N | % |
| 2 | 39 | 19 | 48.7 | 14 | 35.9 | 6 | 15.4 |

| Day 0 Ulcer Diameter | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Total | < 2 mm | | 2 - 4 mm | | > 4 mm | |
| Study | N | N | % | N | % | N | % |
| 2 | 39 | 17 | 43.6 | 20 | 51.3 | 2 | 5.1 |

| Duration | | | | |
|---|---|---|---|---|
| Study | N | Mean | STD | Range |
| 2 | 39 | 4.2 | 4.01 | |

APPEARS THIS WAY
ON ORIGINAL

Efficacy

Microbiology

The culture-positive frequency of Day 0 bacterial corneal scrapings in all 88 enrolled patients was 49% (43/88), with individual investigators exhibiting frequencies of 0% to 100%. Of the culture-positive patients, 39 (90.7%) were evaluative for efficacy. Forty-nine patients did not meet all of the evaluability criteria; forty-three were culture-negative for bacteria, one of whom had a fungus present on entry into the study on Day 0, and five 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 Table 8. Forty-four isolates (21 different species or groups of bacteria) were cultured from the 39 evaluative patients. The organisms most frequently isolated were: *Staphylococcus aureus, S. epidermidis,* and *Pseudomonas aeruginosa.* Other isolates included: *Staphylococcus capitis, S. haemolyticus,* other coagulase-negative staphylococci, *Micrococcus* sp., *Streptococcus pneumoniae, Corynebacterium* spp. (diphtheroids), *Haemophilus influenzae, Serratia marcescens, Serratia liquifaciens, Escherichia coli, Pseudomonas fluorescens, Moraxella (Branhamella) catarrhalis, Moraxella* sp., and *Morganella morganii.* The data for culture-positive corneal ulcers show that gram-positive organisms (68.2%) were more common than gram-negatives (31.8%) (Table 8). Of the gram-positive bacteria, *S. epidermidis* (27.3%) and *S. aureus* (20.5%) constituted about one-half (47.8%) of the isolates. Two of the *S. aureus* strains were methicillin-resistant (MRSAs). Another important organism causing corneal ulcers, *S. pneumoniae,* was isolated from only one (2.8%) of the cases. *P. aeruginosa* was isolated from four (8.3%) ulcers and was the most frequent gram-negative bacteria isolated.

Of the 39 patients evaluative for efficacy, 34 had infections involving only one organism, while five patients were infected with two or more different types of bacteria (polymicrobic). Thirty-six (92%) of the 39 total evaluative patients were judged to be cured or improved regardless of infecting organism type(s). Ciprofloxacin was effective in resolving all five (100%) of the polymicrobic infections. Three of the 34 (8.8%) patients whose ulcers were caused by a single species were treatment failures. One treatment failure case (1606) was infected with a MRSA strain that was reported to be "resistant" to ciprofloxacin, tobramycin and cephalothin, in vitro. The other two patients (1707, 6104) were infected with *S. epidermidis.*

The susceptibility of many of the bacteria isolated in this study to ciprofloxacin is shown in Table 9. Contract laboratory testing showed that 42 of 43 (97.7%) isolates were susceptible to $\leq$ 2.0 $\mu$g/mL ciprofloxacin. The one exception was a MRSA strain, resistant to 4.0 $\mu$g/mL. Twenty-three of the isolates were tested at Alcon and all were found susceptible to $\leq$ 1.5 $\mu$g/mL. The noted ciprofloxacin-resistant MRSA strain was not sent to Alcon.

**Reviewer's Comments:** *In an open label study, lost to follow-up, drop outs and ADR patients should be failures.*

## Evaluability Listing by Patient
## With Microbiological Culture Results

### Study 2

| Inv. No. | Patient No. | Organism(s) Isolated | Study Complete | Physician Judgment | | Evaluative for Efficacy |
|---|---|---|---|---|---|---|
| | | | | On-Therapy | Off-Therapy** | |
| 574 | 201 | *M. morganii* | Yes | Improved | - | Yes/Improved |
| | 202 | Negative | | Cured | - | No/Cured |
| | 203 | *S. haemolyticus; Corynebacterium sp.* | Yes | Cured | Cured | Yes/Cured |
| | 204 | Negative | Yes | Cured | - | No/Cured |
| | 205 | *P. aeruginosa* | Yes | Cured | Cured | Yes/Cured |
| 354 | 301 | *P. aeruginosa* | No | Cured | - | No/LFU |
| | 302 | *S. aureus* | Yes | Cured | Cured | Yes/Cured |
| | 303 | *S. aureus* | Yes | Improved | Cured | Yes/Cured |
| | 304 | *Corynebacterium sp.* | Yes | Cured | - | Yes/Cured |
| | 305 | *S. epidermidis* | Yes | Cured | Cured | Yes/Cured |
| | 306 | *P. aeruginosa* | Yes | Cured | Cured | Yes/Cured |
| | 307 | Negative | | Worse | Worse | No/Worse |
| | 308 | *Moraxella sp.* | Yes | Cured | Cured | Yes/Cured |
| 1117 | 1101 | *P. aeruginosa* | Yes | Cured | Cured | Yes/Cured |
| | 1102 | *Haemophilus influenzae* | Yes | Cured | - | Yes/Cured |
| | 1103 | *S. pneumonia* | Yes | Cured | - | Yes/Cured |
| | 1104 | *S. epidermidis* | Yes | Cured | - | Yes/Cured |
| 1119 | 1201 | *S. aureus* | Yes | Improved | Cured | Yes/Cured |
| | 1202 | Negative | Yes | Cured | Cured | No/Cured |
| 498 | 1601 | *S. marcescens Micrococcus sp. Coag. Neg. Staph.* | Yes | Cured | Cured | Yes/Cured |
| | 1602 | Negative | Yes | Cured | Cured | No/Cured |
| | 1603 | *M. catarrhalis* | Yes | Cured | Cured | Yes/Cured |
| | 1604 | Negative | No | Improved | - | No/LFU |
| | 1605 | Negative | Yes | Cured | - | No/Cured |
| | †*1606 | *S. aureus* | No | Worse | - | Yes/Worse |
| | *1607 | Negative | No | Cured | - | No/Cured |
| | 1608 | *S. warneri; Bacillus sp.* | Yes | Improved | Cured | Yes/Cured |
| | 1609 | Negative | Yes | Improved | - | No/Improved |
| | 1610 | Negative; *T. beigellii* | Yes | Cured | - | No/Fungus |

Continued

| Inv. No. | Patient No. | Organism(s) Isolated | Study Complete | Physician Judgment | | Evaluative for Efficacy |
|---|---|---|---|---|---|---|
| | | | | On-Therapy | Off-Therapy** | |
| 1123 | 1701 | Negative | Yes | Cured | - | No/Cured |
| - | 1702 | *Epicoccum sp.* | Yes | Cured | Cured | No/Fungus |
| | 1703 | *S. epidermidis* | Yes | Cured | Improved | Yes/Improved |
| | 1704 | *S. epidermidis* | Yes | Cured | - | Yes/Cured |
| | 1705 | *S. epidermidis* | Yes | Cured | - | Yes/Cured |
| | 1706 | No Patient | | | | |
| | *1707 | *S. epidermidis* | No | Worse | - | Yes/Worse |
| | 1708 | *S. epidermidis* | Yes | Cured | Cured | Yes/Cured |
| | 1709 | Negative | Yes | Cured | - | Yes/Cured |
| | 1710 | *S. epidermidis* *Coag. Neg. Staph.* | Yes | Cured | - | Yes/Cured |
| | 1711 | *E. cloacae; K. oxytoca* | Yes | Cured | Cured | Yes/Cured |
| | *1712 | Negative | No | Improved | - | No/Improved |
| | 1713 | *S. epidermidis* | Yes | Cured | Cured | Yes/Cured |
| | 1714 | No culture done | No | - | - | No/Not dosed |
| | 1715 | Negative | No | Improved | - | No/Improved |
| 1010 | 2001 | Negative | Yes | Cured | - | No/Cured |
| 1148 | 2101 | Negative | Yes | Cured | - | No/Cured |
| | 2102 | Negative | Yes | Cured | - | No/Cured |
| | 2103 | Negative | Yes | Cured | - | No/Cured |
| 1355 | 2401 | Negative | Yes | Cured | Cured | No/Cured |
| | 2402 | *S. epidermidis* | Yes | Cured | Cured | Yes/Cured |
| | 2403 | *P. fluorescens* | Yes | Cured | Cured | Yes/Cured |
| | 2404 | No Patient | | | | |
| | 2405 | No Patient | | | | |
| | 2406 | *S. aureus* | Yes | Improved | Improved | Yes/Improved |
| 1027 | 2801 | *S. capitis* | Yes | Cured | Cured | Yes/Cured |
| | 2802 | *S. aureus* | Yes | Cured | Cured | Yes/Cured |
| | 2803 | Negative | No | Improved | - | No/LFU |
| | 2804 | Negative | Yes | Cured | - | No/Cured |
| | 2805 | *E. coli* | Yes | Cured | - | Yes/Cured |
| | 2806 | Negative | Yes | Cured | - | No/Cured |

Continued

| Inv. No. | Patient No. | Organism(s) Isolated | Study Complete | Physician Judgment | | Evaluative for Efficacy |
|---|---|---|---|---|---|---|
| | | | | On-Therapy | Off-Therapy** | |
| 635 | 3101 | *S. aureus* | Yes | Cured | Cured | Yes/Cured |
| | 3102 | Negative | Yes | Cured | Cured | No/Cured |
| | 3103 | Negative | Yes | Improved | Cured | No/Cured |
| | 3104 | *S. aureus (MR)* | Yes | Cured | Cured | Yes/Cured |
| | 3105 | Negative | Yes | Cured | Cured | No/Cured |
| | 3106 | Negative | Yes | Cured | Cured | No/Cured |
| | 3107 | *S. aureus* | Yes | Cured | Cured | Yes/Cured |
| | 3108 | Negative | Yes | Cured | Cured | No/Cured |
| | 3109 | Negative | Yes | Improved | Cured | No/Cured |
| 1310 | 3301 | Negative | Yes | Cured | Cured | No/Cured |
| 1001 | 3501 | Negative | Yes | Cured | Cured | No/Cured |
| | 3502 | Negative | Yes | Improved | - | No/Improved |
| | 3503 | Negative | No | Cured | - | No/LFU |
| | 3504 | Negative | Yes | Cured | - | No/Cured |
| | 3505 | *S. epidermidis* | No | Unchanged | - | No/LFU |
| 314 | *4201 | *S. pneumoniae* | No | Unchanged | - | No/Unchanged |
| 1388 | 5801 | *S. liquefaciens* | Yes | Cured | Cured | Yes/Cured |
| | 5802 | Negative | Yes | Cured | Cured | No/Cured |
| | 5803 | Negative | Yes | Cured | - | No/Cured |
| | 5804 | Negative | Yes | Cured | - | No/Cured |
| 798 | 5904 | Negative | Yes | Cured | - | No/Cured |
| 1427 | 6101 | *S. pneumoniae* | No | Cured | - | No/LFU |
| | 6102 | Negative | Yes | Cured | Cured | No/Cured |
| | 6103 | *P. aeruginosa* | Yes | Cured | Cured | Yes/Cured |
| | [1]*6104 | *S. epidermidis* | No | Unchanged | - | Yes/Unchanged |
| | 6105 | Negative | Yes | Cured | - | No/Cured |
| 1007 | 6201 | Negative | Yes | Cured | Cured | No/Cured |
| | 6202 | Negative | Yes | Cured | Cured | No/Cured |
| | 6203 | Negative | Yes | Cured | Cured | No/Cured |
| | *6204 | Negative | No | Improved | - | No/Improved |
| | 6205 | *S. epidermidis* | Yes | Cured | | Yes/Cured |

*Patient discontinued -

**Off-therapy physician judgment - after a minimum of one week off-therapy.

[1]Treatment Failures on Ciprofloxacin Ophthalmic Ointment 0.3%

Clinical

No significant differences were detected between studies for final physician's judgment (p = 0.52). The analysis of physician judgement is presented as follows:

Summary of Final Physician Judgment

| Study | Total | Cured | | Improved | | Unchanged | | Worse | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| 2 | 39 | 33 | 84.6 | 3 | 7.7 | 1 | 2.6 | 2 | 5.4 |

p = 0.52, Cochran-Mantel-Haeszel rank score test

A descriptive summary of final physician's impression by Day 0 size of ulcer and stromal depth is shown in the following table.

Summary of Final Physician Judgment

| Study | Total | Cured | | Improved | | Unchanged | | Worse | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Ulcer Diam < 2 mm | | | | | | | | | |
| 2 | 17 | 15 | 88.2 | - | - | - | - | 2 | 11.8 |
| Ulcer Diam 2-4 mm | | | | | | | | | |
| 2 | 20 | 17 | 85.0 | 3 | 15.0 | - | - | - | - |
| Ulcer Diam > 4 mm | | | | | | | | | |
| 2 | 2 | 1 | 50.0 | - | - | 1 | 50.0 | - | - |
| Superficial | | | | | | | | | |
| 2 | 19 | 19 | 100.0 | - | - | - | - | - | - |
| Mid-Stromal | | | | | | | | | |
| 2 | 14 | 12 | 85.7 | - | - | - | - | 2 | 14.3 |
| Deep Stromal | | | | | | | | | |
| 2 | 6 | 2 | 33.3 | 3 | 50.0 | 1 | 16.7 | - | - |

This table presents the physician's judgment by patient. In addition to tracking effectiveness on a per patient basis, 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.

Cumulative Efficacy Results

| | Cured | | Improved | | Unchanged | | Worse | |
|---|---|---|---|---|---|---|---|---|
| Treatment Phase | 31 | (79.5%) | 5 | (12.8%) | 1* | (2.6%) | 2* | (2.6%) |
| Off-Therapy** | 28 | (93.3%) | 2 | (6.7%) | - | - | - | - |
| Final Evaluation | 33 | (84.6%) | 3 | (7.7%) | 1* | (2.6%) | 2* | (5.1%) |

*These patients are treatment failures.
**Nine patients did not have an off-therapy evaluation.

Thirty six (36) patients (92.3%) benefitted from treatment with Ciprofloxacin Ophthalmic Ointment 0.3% (Cured or Improved) at the final evaluation. The off-therapy evaluation was to determine whether patients who were cured or improved 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 30 (100%) patients that had off-therapy evaluations.

**Reviewer's Comments:** *The above percentages will need to be revised after considering the treatment failures mentioned earlier.*

Safety

Ciprofloxacin Ophthalmic Ointment 0.3% was evaluated for safety in 87 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. These data demonstrate Ciprofloxacin Ophthalmic Ointment 0.3% lacked ophthalmic and systemic toxicity and was well tolerated by patients with bacterial corneal ulcers.

Procedure

Adverse events were obtained as solicited complaints from study subjects and as observations from the Study Investigator. Adverse events were defined as any changes from baseline (expected or unexpected) in a patient's ophthalmic and/or medical health that occurred during the course of the study. Nonserious events were defined as any events that were neither life- or sight-threatening nor serious. Serious events were defined as any events that caused or prolonged hospitalization, were life- or sight-threatening, fatal, permanently disabling, a congenital anomaly, cancer or overdose. Expected events were defined as those changes defined in the Study Investigator's brochure, while unexpected events were defined as not being identified in nature, severity or frequency. All events received independent causality assessments from both the Study Investigator and Medical Monitor. The frequency, incidence and causality assessments of all events are listed in the following table

## Frequency and Incidence of Adverse Events

### Study 2

| Adverse Events | Ciprofloxacin Ophthalmic Ointment 0.3% N=87 | |
|---|---|---|
| | N | % |
| **Ocular** | | |
| White Precipitate | 11 | 12.6 |
| Blurred Vision | 1 | 1.1 |
| Epitheliopathy | 1 | 1.1 |
| Infiltrate | 1 | 1.1 |
| Corneal Erosion | 1 | 1.1 |
| Dry Eye | 1 | 1.1 |
| Perforated Corneal Ulcer | 1.1 | 1.1 |
| | | |
| **Nonocular** | | |
| Skin<br>Dermatitis | 1 | 1.1 |
| Body as a Whole<br>Infection | 1 | 1.1 |
| Accidental Injury | 1 | 1.1 |

Demographics

Demographics for all patients with and without adverse events were analyzed for trends in age, sex and race. Eighteen of the eighty-seven patients (20.7%) 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 reported were generally mild, nonserious and did not interrupt continuation in the study. The most frequently noted ocular event was a white crystalline precipitate in the superficial portion of the corneal defect which was seen in eleven patients (12.6%). 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. Seven of the precipitates were described as white, six were characterized as crystalline precipitates, and six 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 electro-chemical event occurring in the denuded epithelium due to the difference in epithelial cell and quinoline charge. In the eleven patients noted with the event, the onset of the precipitate was within 24 hours to 8 days after starting therapy. In one of the eleven patients, the precipitate was immediately scraped clear. In five patients, resolution was noted in 4 to 13 days without treatment. In two patients, an exact resolution day was unavailable upon exiting the study, as small amounts of precipitate were visible; follow-up examination (19 to 32 days after onset) revealed the precipitate had completely resolved. In the remaining three patients, outcome information was unavailable (one patient was lost to follow-up, one patient still had an ongoing event at exit, one patient was discontinued due to precipitate). The precipitate generally did not interrupt continued use of ciprofloxacin; nine of the eleven patients completed the study as planned (one patient was a treatment failure, one patient was discontinued due to precipitate). 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 reported included blurred vision (1.1%) and epitheliopathy (1.1%). Increased corneal infiltrate (1.1%) in one patient, mild superficial corneal erosion (1.1%), and perforated corneal ulcer was reported in another patient.

Nonocular Events

One patient sensitive to sunlight experienced moderate dermatitis (1.1%) on the forehead, neck and chest possibly related to ciprofloxacin or an idiosyncratic effect. The skin rash occurred on Study Day 13 and resolved in 7 days with oral terfenadine and topical calamine treatment.

Other events reported were; moderate infection on an arm (1.1%) in a diabetic patient and a mild accidental injury (1.1%) when a patient was hit in the eye with a rock.

Serious Events

One serious event (perforated corneal ulcer).

Patients Discontinued Due to Adverse Events

Three patients were discontinued from the study due to adverse events. Two patients were discontinued due to nonserious events (white precipitate, epitheliopathy) related to ciprofloxacin, and one patient was discontinued due to a nonserious event (infection on her arm) unrelated to ciprofloxacin therapy. No patient was discontinued from the study due to a serious treatment-related event.

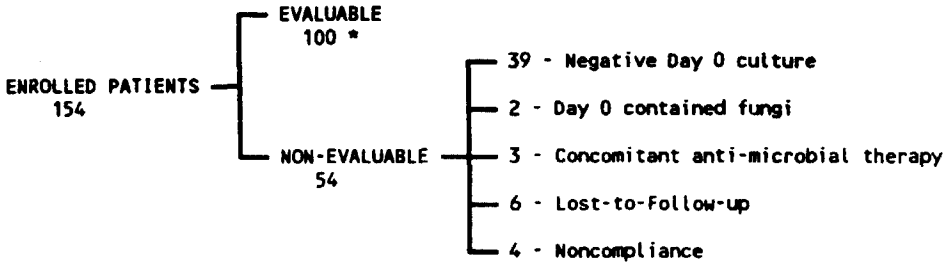
**Multiple Comparisons:**

The results of the of the above studies were compared to three control groups: 1) The Solution Group (C-88-88, NDA 19-992) involved 86 evaluable patients in Study 1 and 62 evaluable patients in Study 2; 2) the Historical control group (C-90-52) involved 71 patients in Study 1 and 32 patients in Study 2 treated with standard antibacterial therapies of the physicians choices within one year prior to the physicians enrolling patients in the solution study C-88-88. (These data was collected retrospectively); 3) the Not Enrolled group consisting of 27 patients in Study 1 and 13 patients in Study 2 who were ineligible for enrollment in the Ciprofloxacin groups because of reasons such as: a)ulcer involves patients only good eye, b) imminent perforation, c)known or suspected fungal keratitis, d) patients who refuse treatment with ciprofloxacin and were treated with standard therapy.

## Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - Study 1

### Ciprofloxacin Solution (C-88-88) Enrollment - STUDY 1

| | EVALUABLE | |
|---|---|---|
| INV | NO | YES |
| 331 | 3 | - |
| 362 | 8 | 8 |
| 372 | 6 | 9 |
| 557 | 2 | 13 |
| 845 | 3 | 11 |
| 870 | 5 | 6 |
| 871 | 10 | 7 |
| 1019 | - | 6 |
| 1053 | 2 | - |
| 1108 | 5 | 20 |
| 1121 | 1 | 4 |
| 1128 | 8 | 14 |
| 1164 | 1 | - |
| 1189 | - | 2 |
| TOTAL | 54 | 100 |




* Used in All Statistical Analyses

**Reviewer's Comments:** *An explanation for the discrepancy between the number of evaluable patients (100) in study C-88-88-1 and the 86 which were actually used in all statistical analyses was requested from the sponsor. The response was that these 86 patients were the group analyzed for the NDA submission for the solution (NDA 19-992). This is unacceptable.*

Patient Demographics and Day 0 Ulcer Characteristics for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 1

No significant differences were found for age, sex or race ($p>0.32$). Additionally, no significant differences were observed at Day 0 for ulcer duration, ulcer depth or ulcer size ($p>0.09$).

| AGE: | N | MEAN | STD |
|---|---|---|---|
| Soln | 86 | 51.0 | 22.67 |
| Oint | 105 | 51.1 | 22.94 |

p=0.99, One-way ANOVA

| SEX: | Male | | Female | |
|---|---|---|---|---|
| | N | % | N | % |
| Soln | 40 | 46.5 | 46 | 53.5 |
| Oint | 57 | 53.8 | 49 | 46.2 |

p=0.32, Chi-square test for independence

| RACE: | CAUCASIAN | | BLACK | | OTHER | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Soln | 47 | 54.7 | 18 | 20.9 | 21 | 24.4 |
| Oint | 57 | 53.8 | 23 | 21.7 | 26 | 24.5 |

p=0.99, Chi-square test for independence

| DURATION (days): | N | MEAN | STD |
|---|---|---|---|
| Soln | 86 | 9.4 | 14.69 |
| Oint | 106 | 6.9 | 9.54 |

p=0.16, One-way ANOVA

| DAY 0 STROMAL DEPTH OF ULCER | Superficial | | Mid-Stromal | | Deep Stromal | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Soln | 33 | 38.4 | 27 | 31.4 | 26 | 30.2 |
| Oint | 49 | 46.2 | 38 | 35.8 | 19 | 17.9 |

p=0.10, Cochran-Mantel-Haenszel rank score test

| DAY 0 ULCER DIAM. | < 2 mm | | 2 - 4 mm | | > 4 mm | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Soln | 22 | 25.6 | 36 | 41.9 | 28 | 32.6 |
| Oint | 34 | 32.1 | 50 | 47.2 | 22 | 20.8 |

p=0.09, Cochran-Mantel-Haenszel rank score test

**Reviewer's Comments:** *The Ciprofloxacin solution group has a trend to have a more serious ulcer.*

## Comparison of Physician's Final Judgement for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 1

| | TOTAL N | CURED N | CURED % | IMPROVED N | IMPROVED % | UNCHANGED N | UNCHANGED % | WORSE N | WORSE % | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Solution | 86 | 62 | 72.1 | 18 | 20.9 | 3 | 3.5 | 3 | 3.5 | <.01* |
| Ointment | 106 | 94 | 88.7 | 5 | 4.7 | 4 | 3.8 | 3 | 2.8 | |
| **Day 0 Ulcer Diameter < 2 mm** | | | | | | | | | | |
| Solution | 22 | 15 | 68.2 | 3 | 13.6 | 2 | 9.1 | 2 | 9.1 | 0.01** |
| Ointment | 34 | 33 | 97.1 | 1 | 2.9 | - | - | - | - | |
| **Day 0 Ulcer Diameter 2 - 4 mm** | | | | | | | | | | |
| Solution | 36 | 27 | 75.0 | 9 | 25.0 | - | - | - | - | |
| Ointment | 50 | 46 | 92.0 | 1 | 2.0 | 2 | 4.0 | 1 | 2.0 | |
| **Day 0 Ulcer Diameter > 4 mm** | | | | | | | | | | |
| Solution | 28 | 20 | 71.4 | 6 | 21.4 | 1 | 3.6 | 1 | 3.6 | |
| Ointment | 22 | 15 | 68.2 | 3 | 13.6 | 2 | 9.1 | 2 | 9.1 | |

* Cochran-Mantel-Haenszel rank score test
** Cochran-Mantel-Haenszel rank score test controlling for Day 0 Ulcer Size

Physicians in STUDY 1 judged Ciprofloxacin ointment to be significantly more effective for the treatment of corneal ulcers than Ciprofloxacin solution ($p<0.01$). An additional analysis was performed to insure that cure rates were not dependent on ulcer size. This analysis indicated that Ciprofloxacin ointment was significantly more effective than Ciprofloxacin solution ($p=0.01$) after adjusting for ulcer size.

**Reviewer's Comments:** *The percentages for the ointment group needs to be revised.*

## Comparison of Days on Treatment & Treatment Failures for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 1

| | DAYS ON TREATMENT N | MEAN | STD |
|---|---|---|---|
| Soln | 86 | 20.9 | 16.02 |
| Oint | 105 | 18.8 | 10.37 |

p=0.26, One-way ANOVA

| | TREATMENT FAILURES NO N | NO % | YES N | YES % |
|---|---|---|---|---|
| Soln | 79 | 91.9 | 7 | 8.1 |
| Oint | 99 | 93.4 | 7 | 6.6 |

p=0.68, Chi-square test for independence

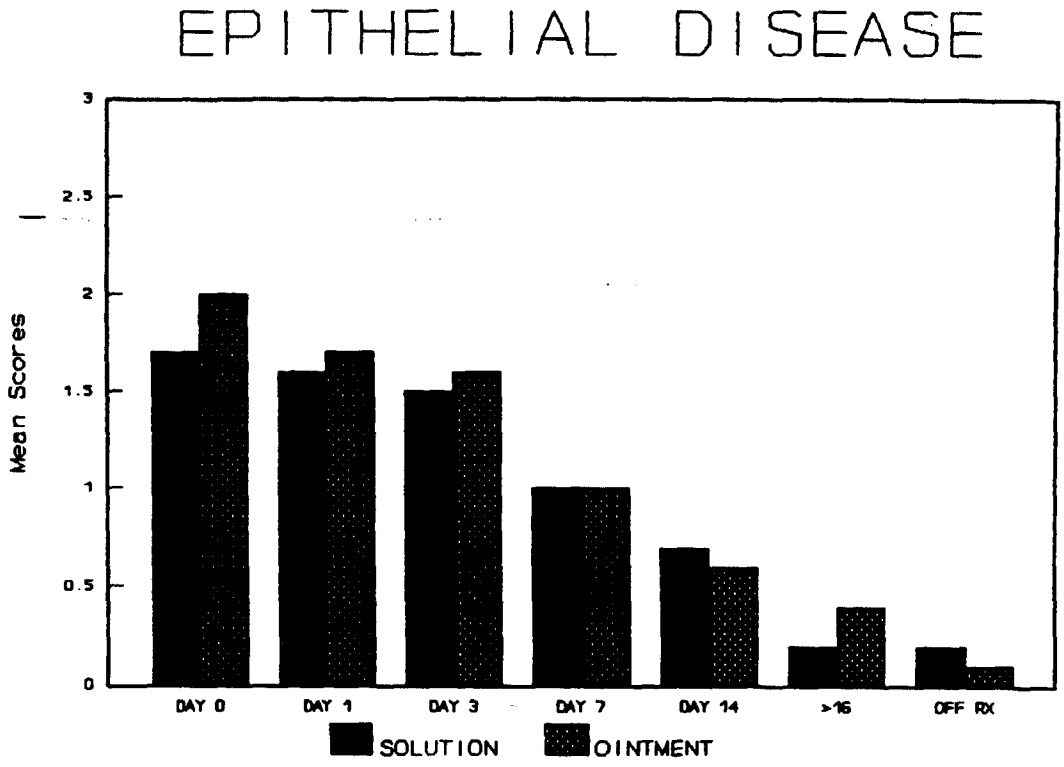
No significant treatment differences were observed for the number of days patients were on therapy ($p=0.26$) or the percentage of treatment failures ($p=0.68$).

**Reviewer's Comments:** *Concur.*

**Comparison of Major Clinical Signs Associated with Corneal Ulcers for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 1**

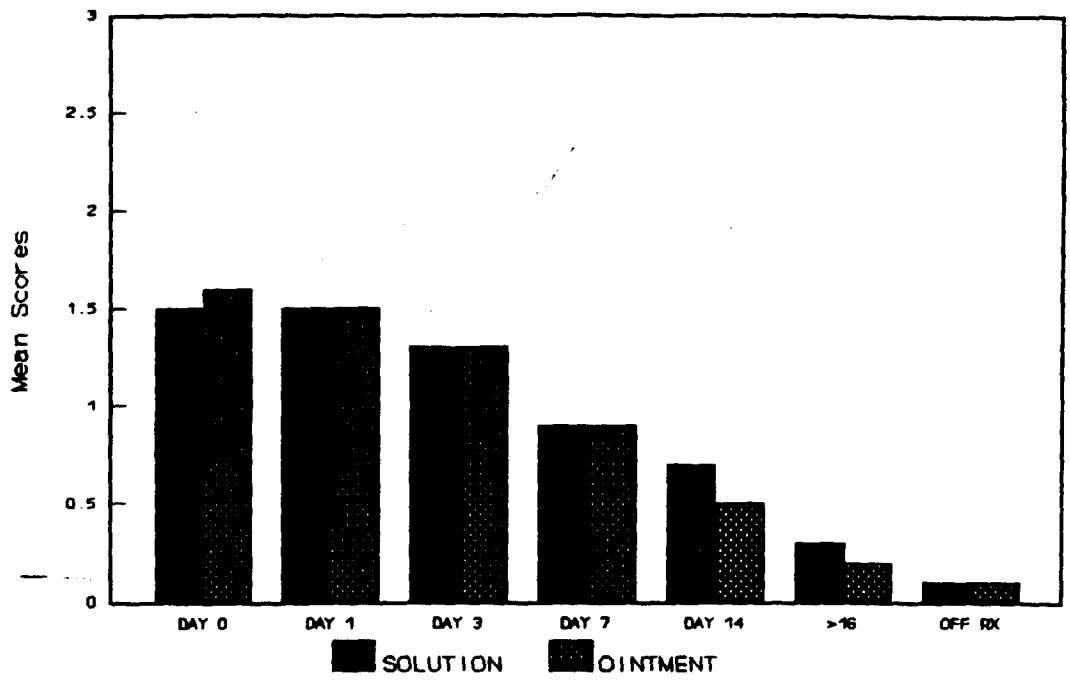
Six major clinical signs of corneal ulcers, epithelial disease, focal stromal infiltrates, aqueous cells, aqueous flare, conjunctival discharge and erythema.

**Reviewer's Comments:** *The following graphs were constructed with the data submitted. Ciprofloxacin ointment is not clinically different from Ciprofloxacin solution at off-therapy for all major clinical signs.*

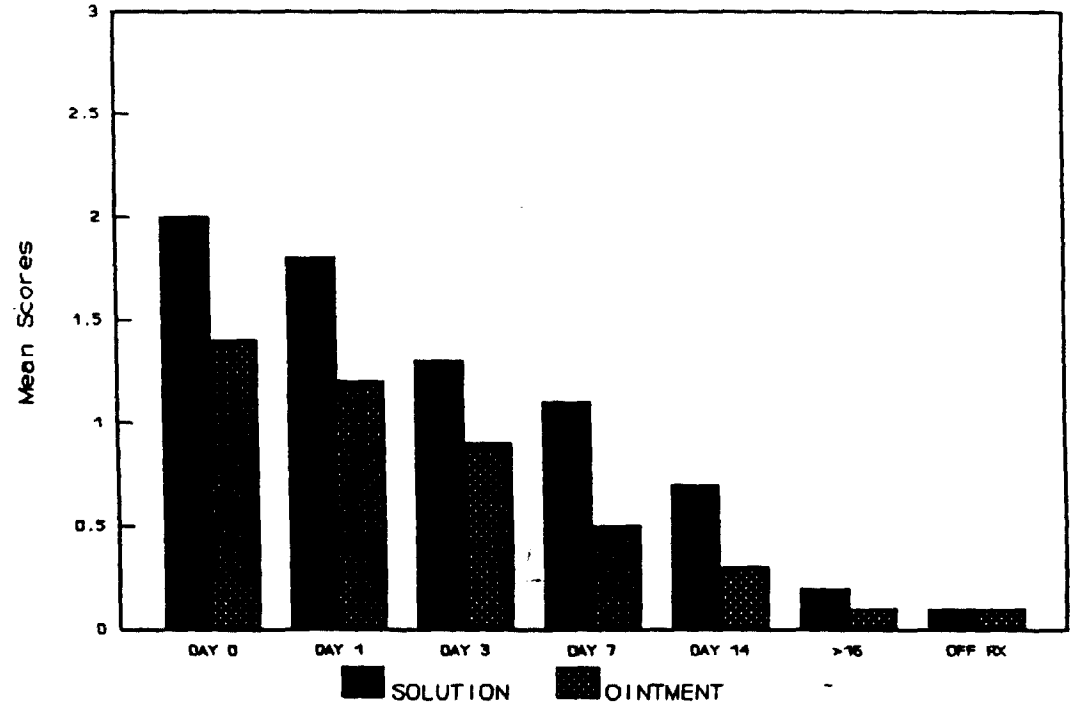


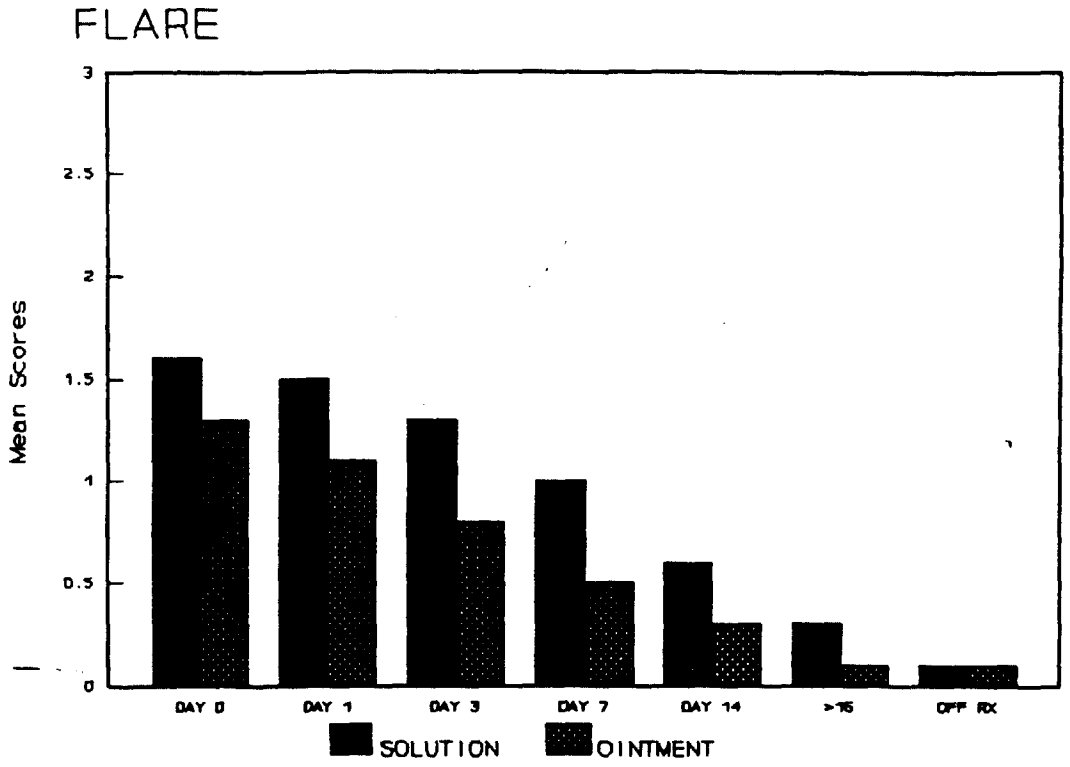

APPEARS THIS WAY
ON ORIGINAL

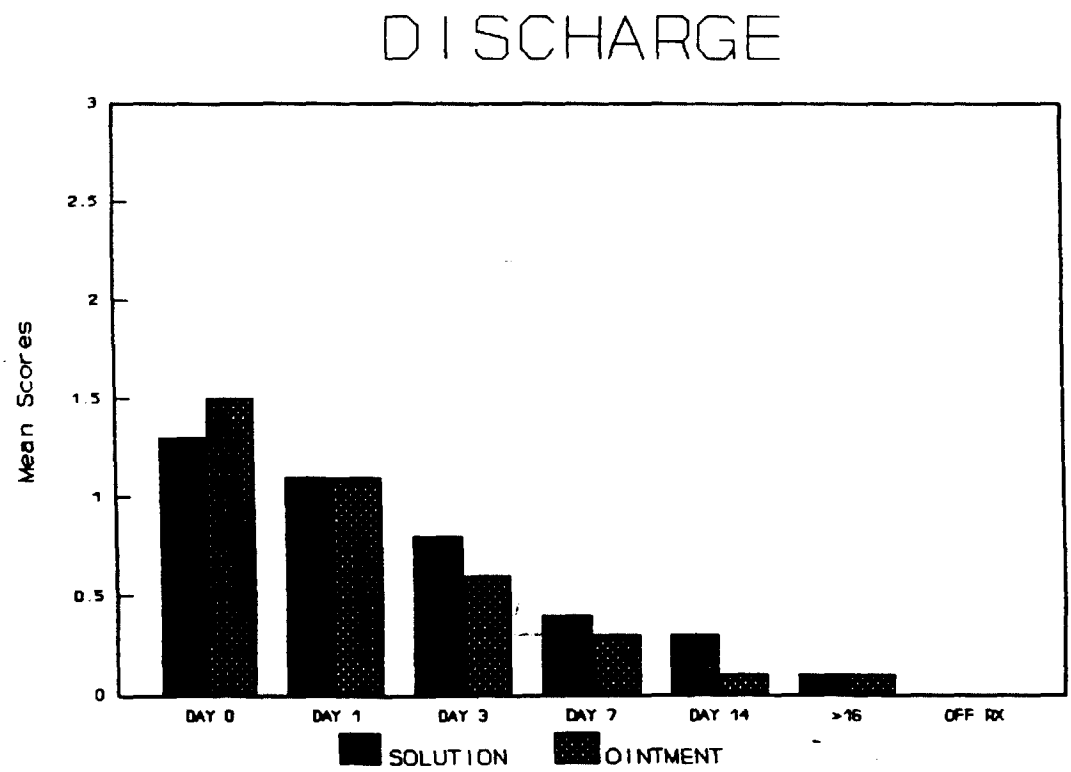
# FOCAL INFILTRATES



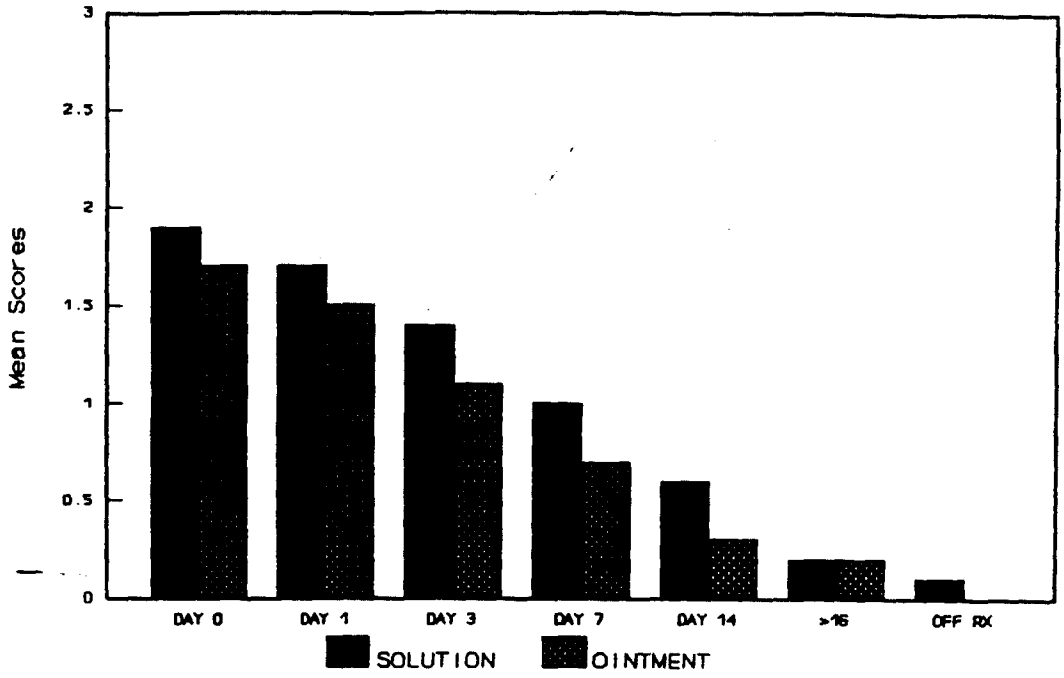

# CELLS




FLARE
Mean Scores
3
2.5
2
1.5
1
0.5
0
DAY 0
DAY 1
DAY 3
DAY 7
DAY 14
>16
OFF RX
SOLUTION
OINTMENT


DISCHARGE
Mean Scores
3
2.5
2
1.5
1
0.5
0
DAY 0
DAY 1
DAY 3
DAY 7
DAY 14
>16
OFF RX
SOLUTION
OINTMENT

# ERYTHEMA




APPEARS THIS WAY
ON ORIGINAL

## Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 1

The following analyses compare data for 106 Ciprofloxacin Ointment patients to 27 standard therapy patients from Protocol C-90-94. **All analytical results should be interpreted with some degree of caution due to the small number of standard therapy patients.**

### Patient Demographics and Day 0 Ulcer Characteristics for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 1

No significant differences were found for age, sex or race ($p > 0.23$) or Day 0 ulcer diameter, depth or duration ($p > 0.17$).

| SEX: | MALE | | FEMALE | |
|---|---|---|---|---|
| | N | % | N | % |
| Oint | 57 | 53.8 | 49 | 46.2 |
| Std Tx | 17 | 63.0 | 10 | 37.0 |

p=0.39, Chi-square test for independence

| RACE: | Caucasian | | Black | | Other | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Oint | 57 | 53.8 | 23 | 21.7 | 26 | 24.5 |
| Std Tx | 18 | 66.7 | 5 | 18.5 | 4 | 14.8 |

p=0.44, Chi-square test for independence

| AGE: | N | MEAN | STD |
|---|---|---|---|
| Oint | 105 | 51.1 | 22.94 |
| Std Tx | 26 | 45.2 | 19.62 |

p=0.23, One-way ANOVA

| DAY 0 ULCER DIAM | < 2 mm | | 2 - 4 mm | | > 4 mm | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Oint | 34 | 32.1 | 50 | 47.2 | 22 | 20.8 |
| Std Tx | 13 | 48.1 | 9 | 33.3 | 5 | 18.5 |

p=0.22, Cochran-Mantel-Haenszel rank score test

| DAY 0 STROMAL DEPTH OF ULCER | Superficial | | Mid-Stromal | | Deep Stromal | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Oint | 49 | 46.2 | 38 | 35.8 | 19 | 17.9 |
| Std Tx | 10 | 37.0 | 10 | 37.0 | 7 | 25.9 |

p=0.31, Cochran-Mantel-Haenszel rank score test

| DURATION | N | MEAN | STD |
|---|---|---|---|
| Oint | 106 | 6.9 | 9.54 |
| Std Tx | 27 | 4.3 | 3.87 |

p=0.17, One-way ANOVA

**Comparison of Physician's Final Judgement for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 1**

| | | FINAL IMPRESSION | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TOTAL | CURED | | IMPROVED | | UNCHANGED | | WORSE | | |
| | N | N | % | N | % | N | % | N | % | p-value |
| Oint | 106 | 94 | 88.7 | 5 | 4.7 | 4 | 3.8 | 3 | 2.8 | <0.01* |
| Std Tx | 27 | 18 | 66.7 | 6 | 22.2 | 2 | 7.4 | 1 | 3.7 | |
| Ulcer Diam < 2 mm | | | | | | | | | | |
| Oint | 34 | 33 | 97.1 | 1 | 2.9 | - | - | - | - | <0.01** |
| Std Tx | 13 | 11 | 84.6 | 2 | 15.4 | - | - | - | - | |
| Ulcer Diam 2 - 4 mm | | | | | | | | | | |
| Oint | 50 | 46 | 92.0 | 1 | 2.0 | 2 | 4.0 | 1 | 2.0 | |
| Std Tx | 9 | 5 | 55.6 | 2 | 22.2 | 1 | 11.1 | 1 | 11.1 | |
| Ulcer Diam > 4 mm | | | | | | | | | | |
| Oint | 22 | 15 | 68.2 | 3 | 13.6 | 2 | 9.1 | 2 | 9.1 | |
| Std Tx | 5 | 2 | 40.0 | 2 | 40.0 | 1 | 20.0 | - | - | |

* Cochran-Mantel-Haenszel rank score test
** Cochran-Mantel-Haenszel rank score test controlling for Day 0 ulcer size

Sponsor's Report: Physicians judged Ciprofloxacin ointment to be significantly more effective for the treatment of corneal ulcers than standard therapy ($p<0.01$). An additional analysis was performed to insure that cure rates were not dependent on ulcer size. This analysis indicated that Ciprofloxacin Ointment was significantly more effective than standard therapy for the treatment of corneal ulcers ($p < 0.01$) after adjusting for ulcer size.

**Reviewer's Comments:** *All analytical results should be interpreted with some degree of caution due to the small number of standard therapy patients.*

**Comparison of Days on Treatment & Treatment Failures for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 1**

| | DAYS ON DRUG | | |
|---|---|---|---|
| | N | MEAN | STD |
| Oint | 105 | 18.8 | 10.37 |
| Std Tx | 26 | 24.7 | 18.53 |

p=0.03, One-way ANOVA

| | Treatment Failed | | | |
|---|---|---|---|---|
| | No | | Yes | |
| | N | % | N | % |
| Oint | 99 | 93.4 | 7 | 6.6 |
| Std Tx | 18 | 66.7 | 9 | 33.3 |

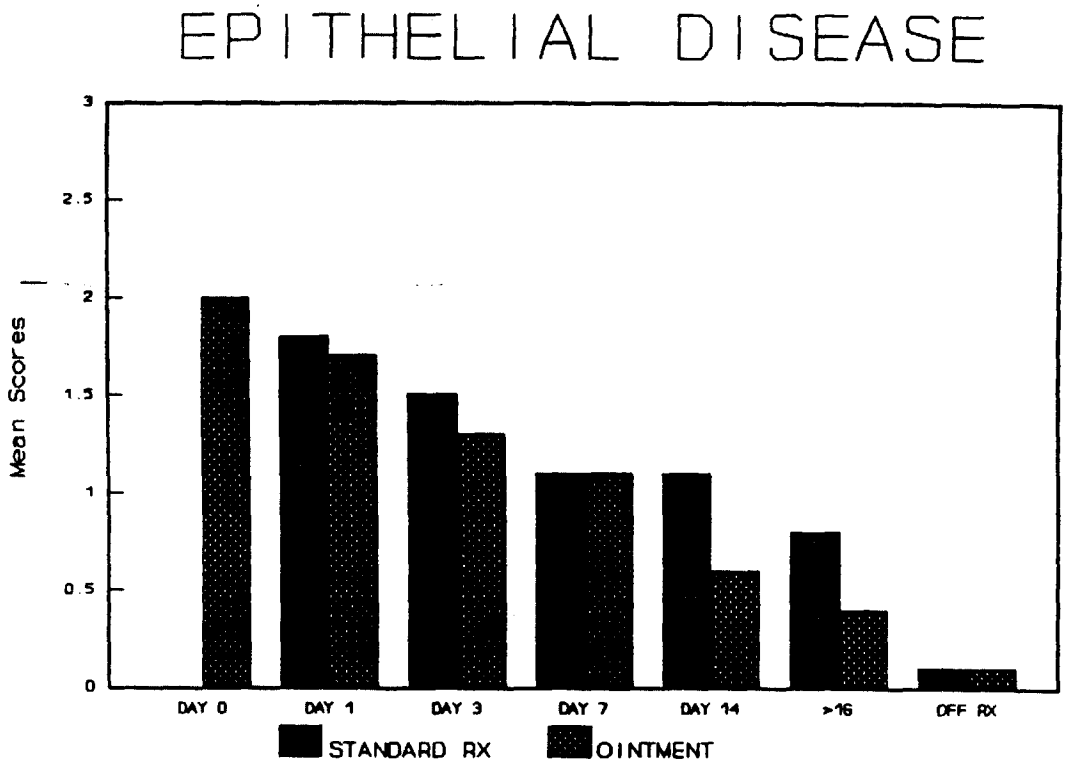
p<0.001, Fisher's Exact test

Patients on Standard Therapy were on treatment significantly longer than Ciprofloxacin ointment patients ($p = 0.03$). Significantly more non-enrolled patients on standard therapy were treatment failures ($p < 0.001$).

**Reviewer's Comments:** *All analytical results should be interpreted with some degree of caution due to the small number of standard therapy patients.*

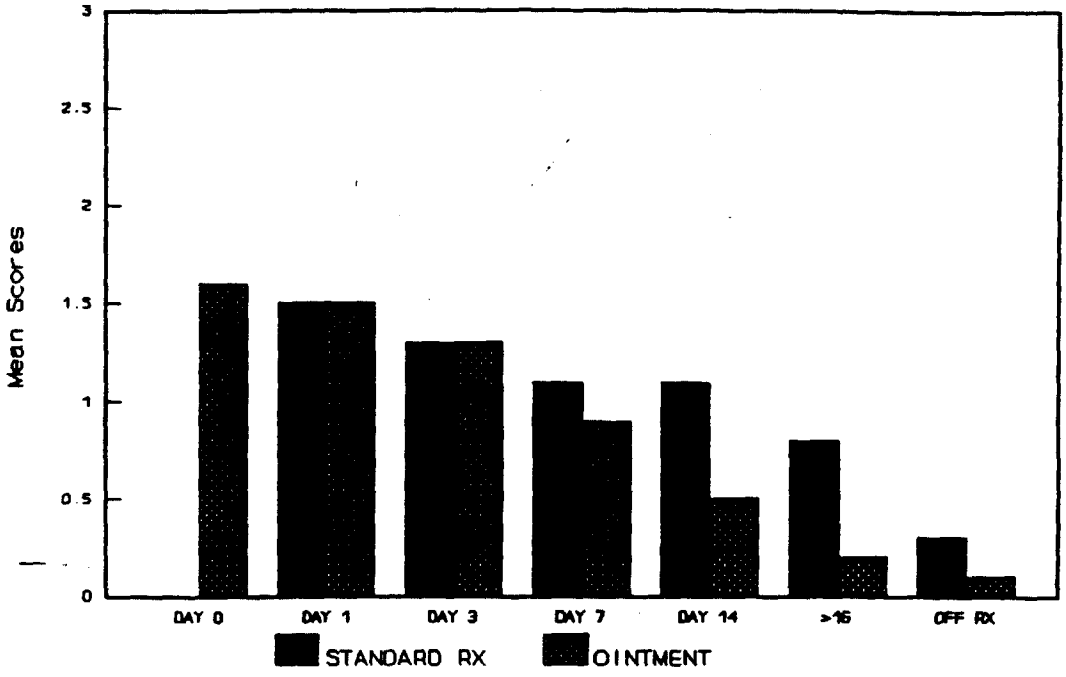
**Comparison of Major Clinical Signs Associated with Corneal Ulcers for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 1**

**Reviewer's Comments:** *The following graphs were constructed with the data submitted. Clinically Ciprofloxacin ointment is not significantly different from Standard therapy at off-therapy for all major clinical signs.*

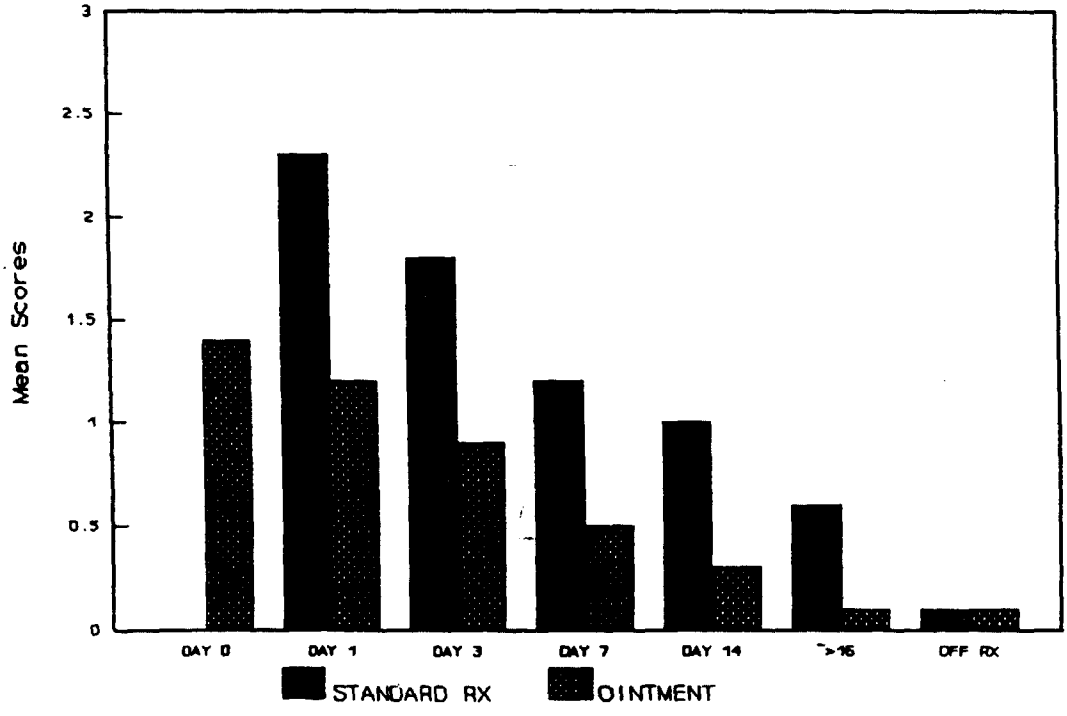


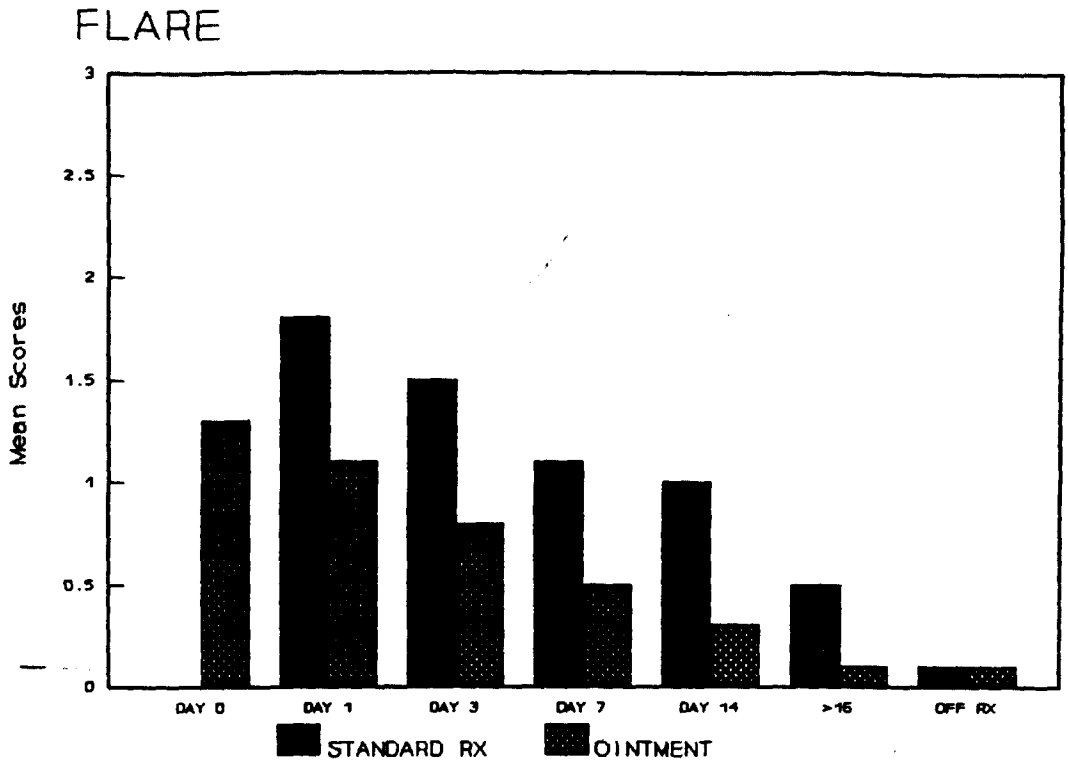

APPEARS THIS WAY
ON ORIGINAL

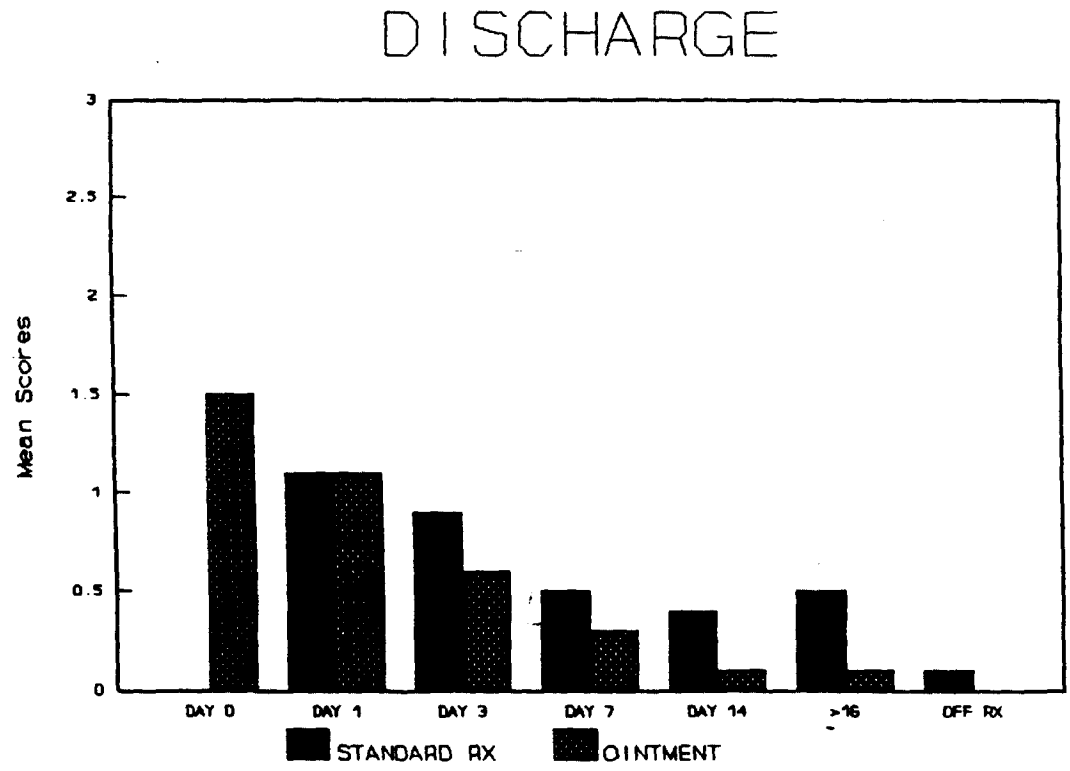
# FOCAL INFILTRATES



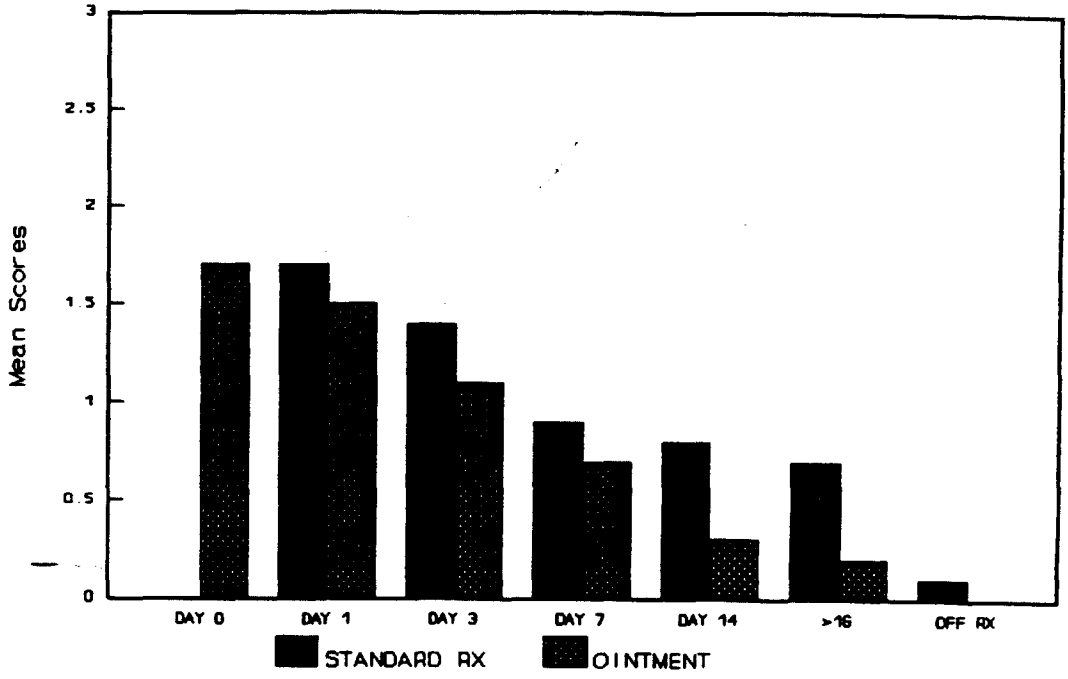

# CELLS




FLARE
Mean Scores
3
2.5
2
1.5
1
0.5
0
DAY 0
DAY 1
DAY 3
DAY 7
DAY 14
>16
OFF RX
STANDARD RX
OINTMENT


DISCHARGE
Mean Scores
3
2.5
2
1.5
1
0.5
0
DAY 0
DAY 1
DAY 3
DAY 7
DAY 14
>16
OFF RX
STANDARD RX
OINTMENT

# ERYTHEMA




APPEARS THIS WAY
ON ORIGINAL

## Ciprofloxacin Ointment (C-90-85) vs Historical Patients (C-90-52) - STUDY 1

The following analyses compare data for 106 Ciprofloxacin Ointment patients to 71 historical database patients who were on standard therapy (C-90-52). The historical database was based on retrospective data obtained from physician records of corneal ulcer patients who received standard therapy within one year prior to the investigator enrolling patients into the Ciprofloxacin solution study. Ocular signs and symptoms, Day 0 ulcer depth and location and demographics were not collected for historical patients.

### Day 0 Longest Ulcer Diameter (mm) for Ciprofloxacin Ointment (C-90-85) vs Historical (C-90-52) - STUDY 1

Historical standard therapy patients had significantly more ulcers > 4 mm than patients on Ciprofloxacin Ointment ($p<0.001$).

| Day 0 Ulcer Diam | < 2 mm N | % | 2 - 4 mm N | % | > 4 mm N | % |
|---|---|---|---|---|---|---|
| Oint | 34 | 32.1 | 50 | 47.2 | 22 | 20.8 |
| Hist | 7 | 9.9 | 39 | 54.9 | 25 | 35.2 |

p<0.001, Cochran-Mantel-Haenszel rank score test

### Comparison of Physician's Final Judgement for STUDY 1

| | | FINAL IMPRESSION | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TOTAL N | CURED N | % | IMPROVED N | % | UNCHANGED N | % | WORSE N | % | p-value |
| Oint | 106 | 94 | 88.7 | 5 | 4.7 | 4 | 3.8 | 3 | 2.8 | <0.001* |
| Hist | 71 | 41 | 57.7 | 23 | 32.4 | 3 | 4.2 | 4 | 5.6 | |
| **Ulcer Diam. < 2 mm** | | | | | | | | | | |
| Oint | 34 | 33 | 97.1 | 1 | 2.9 | - | - | - | - | <0.001** |
| Hist | 7 | 7 | 100.0 | - | - | - | - | - | - | |
| **Ulcer Diam. 2-4 mm** | | | | | | | | | | |
| Oint | 50 | 46 | 92.0 | 1 | 2.0 | 2 | 4.0 | 1 | 2.0 | |
| Hist | 39 | 23 | 59.0 | 13 | 33.3 | 1 | 2.6 | 2 | 5.1 | |
| **Ulcer Diam. > 4 mm** | | | | | | | | | | |
| Oint | 22 | 15 | 68.2 | 3 | 13.6 | 2 | 9.1 | 2 | 9.1 | |
| Hist | 25 | 11 | 44.0 | 10 | 40.0 | 2 | 8.0 | 2 | 8.0 | |

* Cochran-Mantel-Haenszel rank score test
** Cochran-Mantel-Haenszel rank score test, controlling for Day 0 Ulcer Size

Sponsor's Report: Physicians judged Ciprofloxacin ointment to be significantly more effective for the treatment of corneal ulcers than historical standard therapy ($p<0.001$). Since the Historical study had significantly more patients with ulcer diameters larger than 4 mm, a second analysis, to adjust for differences in ulcer diameter, indicated Ciprofloxacin ointment to be significantly more effective for the treatment of corneal ulcers than standard therapy ($p<0.001$).

**Reviewer's Comments:** *Concur*

**Comparison of Days on Treatment & Treatment Failures for Ciprofloxacin Ointment (C-90-85) vs Historical (C-90-52) - STUDY 1**

Days on Treatment

| | N | MEAN | STD | MIN | MAX |
|---|---|---|---|---|---|
| Oint | 105 | 18.8 | 10.37 | | |
| Hist | 69 | 51.1 | 81.41 | | |

p<0.001, Two-sample t-test

Treatment Failed

| | NO | | YES | |
|---|---|---|---|---|
| | N | % | N | % |
| Oint | 99 | 93.4 | 7 | 6.6 |
| Hist | 51 | 71.8 | 20 | 28.2 |

p<0.001, Chi-square test for independence

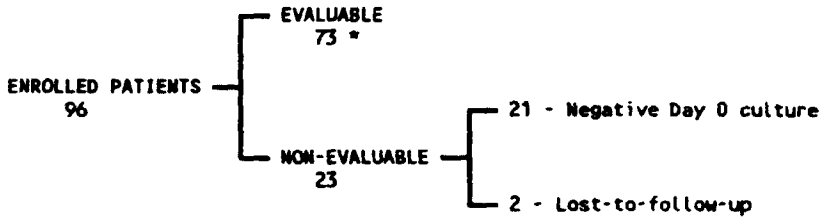
Sponsor's Report: Historical standard therapy patients were on treatment significantly longer than patients on Ciprofloxacin Ointment ($p < 0.001$). Historical standard therapy patients had significantly more treatment failures ($p < 0.001$).

**Reviewer's Comments:** *Concur*

## Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 2

### Ciprofloxacin Solution (C-88-88) Enrollment - Study 2

| | EVALUABLE | |
|---|---|---|
| INV | NO | YES |
| 354 | - | 9 |
| 498 | 7 | 12 |
| 574 | 1 | 17 |
| 635 | 1 | - |
| 798 | 1 | - |
| 1025 | - | 3 |
| 1027 | 7 | 3 |
| 1110 | 1 | 9 |
| 1112 | - | 1 |
| 1117 | 3 | 4 |
| 1119 | - | 5 |
| 1123 | 1 | 9 |
| 1148 | 1 | 1 |
| TOTAL | 23 | 73 |




* Used in All Statistical Analyses

**Reviewer's Comments:** *An explanation for the discrepancy between the number of evaluable patients (73) in study C-88-88 and the 62 which were actually used in all statistical analyses was requested from the sponsor. The response was that these 62 patients were the group analized for the NDA submission for the solution (NDA 19-992). This is unacceptable.*

The following analyses compare data for 39 Ciprofloxacin Ointment patients to 62 Ciprofloxacin Solution patients.

**Patient Demographics and Day 0 Ulcer Characteristics for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 2**

No significant differences were found for age, sex or race ($p > 0.35$). Ciprofloxacin solution treated patients had significantly more ulcer diameters larger than 4 mm. ($p = 0.049$), but no significant differences were observed at Day 0 for ulcer duration or ulcer depth ($p > 0.14$).

| AGE: | N | MEAN | STD |
|---|---|---|---|
| Soln | 62 | 45.9 | 22.86 |
| Oint | 39 | 44.5 | 23.06 |

p=0.78, One-way ANOVA

| SEX: | Male | | Female | |
|---|---|---|---|---|
| | N | % | N | % |
| Soln | 32 | 51.6 | 30 | 48.4 |
| Oint | 19 | 48.7 | 20 | 51.3 |

p=0.78, Chi-square test for independence

| RACE: | CAUCASIAN | | BLACK | | ASIAN | | OTHER | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Soln | 45 | 72.6 | 8 | 12.9 | 1 | 1.6 | 8 | 12.9 |
| Oint | 32 | 82.1 | 1 | 2.6 | 1 | 2.6 | 5 | 12.8 |

p=0.35, Chi-square test for independence

| DURATION (days): | N | MEAN | STD |
|---|---|---|---|
| Soln | 62 | 7.4 | 12.91 |
| Oint | 39 | 4.2 | 4.01 |

p=0.14, One-way ANOVA

| DAY 0 STROMAL DEPTH OF ULCER | Superficial | | Mid-Stromal | | Deep Stromal | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Soln | 32 | 51.6 | 23 | 37.1 | 7 | 11.3 |
| Oint | 19 | 48.7 | 14 | 35.9 | 6 | 15.4 |

p=0.67, Cochran-Mantel-Haenszel rank score test

| DAY 0 ULCER DIAM. | < 2 mm | | 2 - 4 mm | | > 4 mm | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Soln | 20 | 32.3 | 27 | 43.5 | 15 | 24.2 |
| Oint | 17 | 43.6 | 20 | 51.3 | 2 | 5.1 |

p=0.049, Cochran-Mantel-Haenszel rank score test

**Reviewer's Comments:** *The solution group had more patients with larger ulcers than the ointment group.*

**Comparison of Physician's Final Judgement for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 2**

| | TOTAL N | CURED N | CURED % | IMPROVED N | IMPROVED % | UNCHANGED N | UNCHANGED % | WORSE N | WORSE % | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Solution | 62 | 51 | 82.3 | 5 | 8.1 | 3 | 4.8 | 3 | 4.8 | 0.76* |
| Ointment | 39 | 33 | 84.6 | 3 | 7.7 | 1 | 2.6 | 2 | 5.1 | |
| **Day 0 Ulcer Diameter < 2 mm** | | | | | | | | | | |
| Solution | 20 | 18 | 90.0 | 1 | 5.0 | 1 | 5.0 | - | - | 0.92** |
| Ointment | 17 | 15 | 88.2 | - | - | - | - | 2 | 11.8 | |
| **Day 0 Ulcer Diameter 2 - 4 mm** | | | | | | | | | | |
| Solution | 27 | 22 | 81.5 | 4 | 14.8 | - | - | 1 | 3.7 | |
| Ointment | 20 | 17 | 85.0 | 3 | 15.0 | - | - | - | - | |
| **Day 0 Ulcer Diameter > 4 mm** | | | | | | | | | | |
| Solution | 15 | 11 | 73.3 | - | - | 2 | 13.3 | 2 | 13.3 | |
| Ointment | 2 | 1 | 50.0 | - | - | 1 | 50.0 | - | - | |

* Cochran-Mantel-Haenszel rank score test
** Cochran-Mantel-Haenszel rank score test controlling for Day 0 Ulcer Size

No significant treatment differences were detected for physician's final judgement in STUDY 2 (p=0.76). Since the Ciprofloxacin solution study had significantly more patients with ulcer diameters larger than 4 mm, a second analysis, to adjust for differences in ulcer diameter, was performed. No significant treatment differences were found after adjusting for ulcer size (p=0.92).

**Reviewer's Comments:** *This study does not have enough large ulcers to make a determination.*

**Comparison of Days on Treatment & Treatment Failures for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 2**

| | DAYS ON TREATMENT N | MEAN | STD |
|---|---|---|---|
| Soln | 62 | 22.4 | 22.51 |
| Oint | 39 | 16.8 | 8.72 |

p=0.14, One-way ANOVA

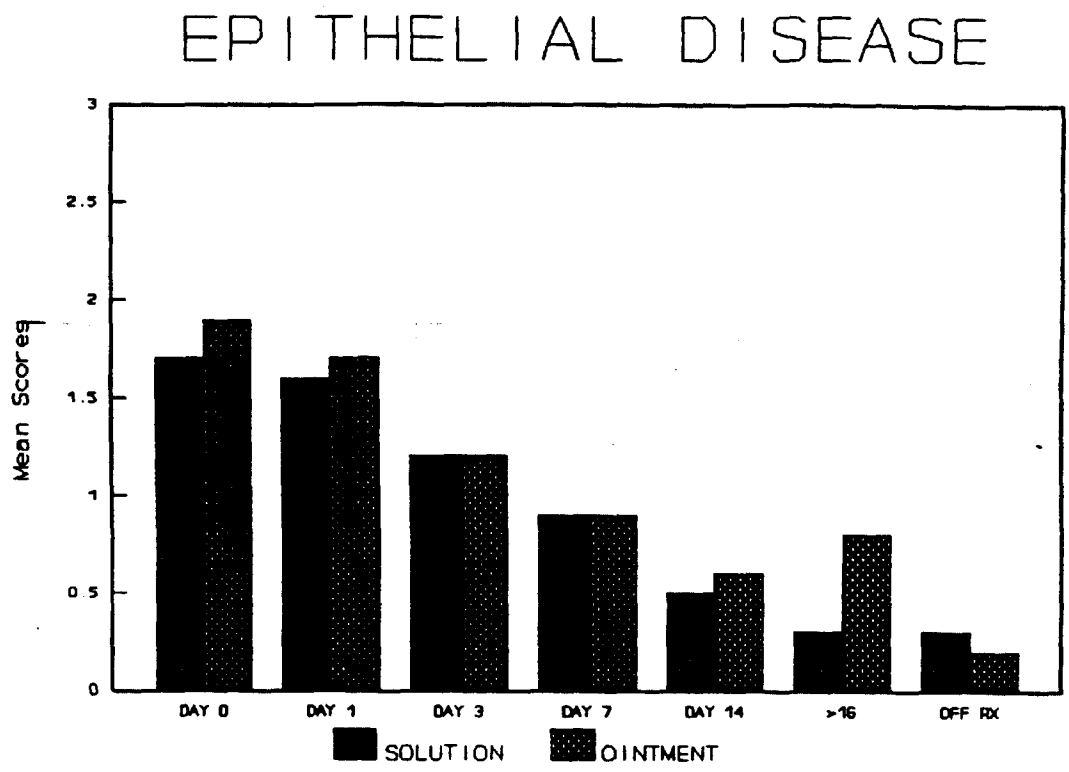
| | TREATMENT FAILURES NO N | NO % | YES N | YES % |
|---|---|---|---|---|
| Soln | 57 | 91.9 | 5 | 8.1 |
| Oint | 36 | 92.3 | 3 | 7.7 |

p=0.95, Chi-square test for independence

No significant treatment differences were observed for the number of days patients were on therapy (p=0.14) or the percentage of treatment failures (p=0.95).

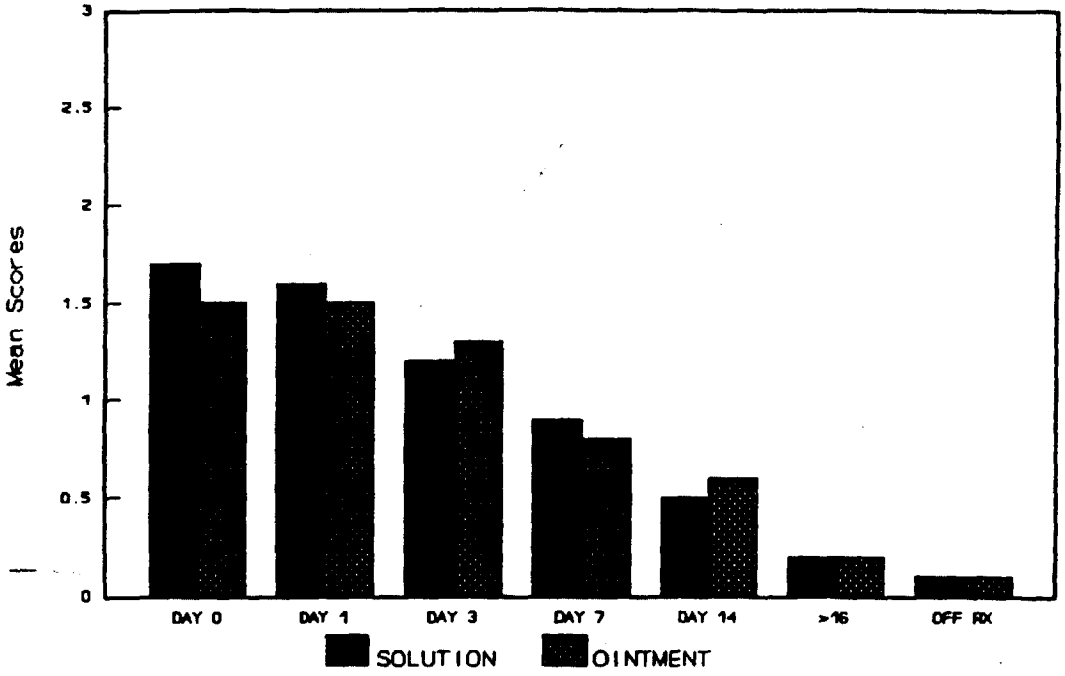
**Comparison of Major Clinical Signs Associated with Corneal Ulcers for Ciprofloxacin Ointment (C-90-85) vs Ciprofloxacin Solution (C-88-88) - STUDY 2**

**Reviewer's Comments:** *The following graphs were constructed with the data submitted. Ciprofloxacin ointment is not clinically different from Ciprofloxacin solution at off-therapy for all major clinical signs.*

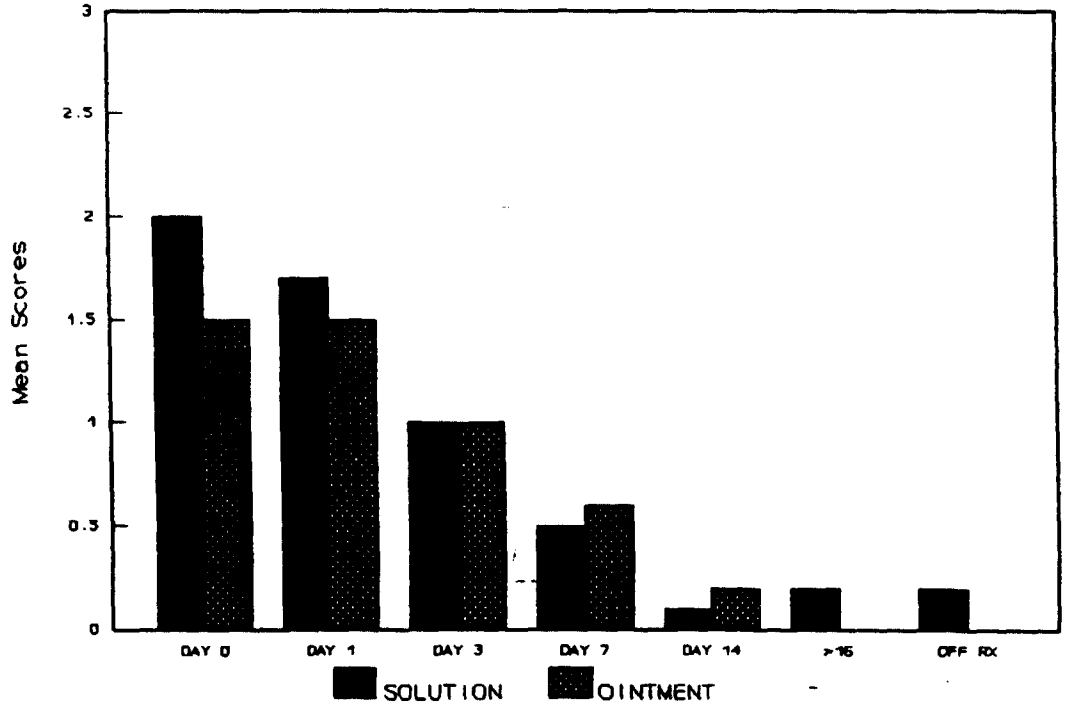



APPEARS THIS WAY
ON ORIGINAL

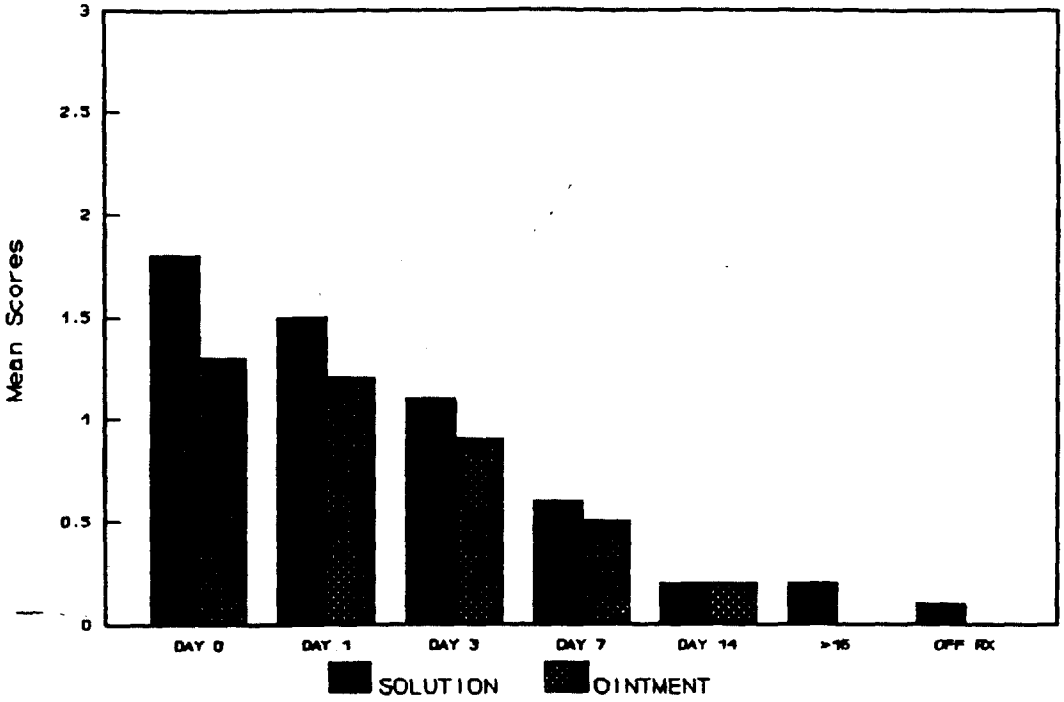
# FOCAL INFILTRATES



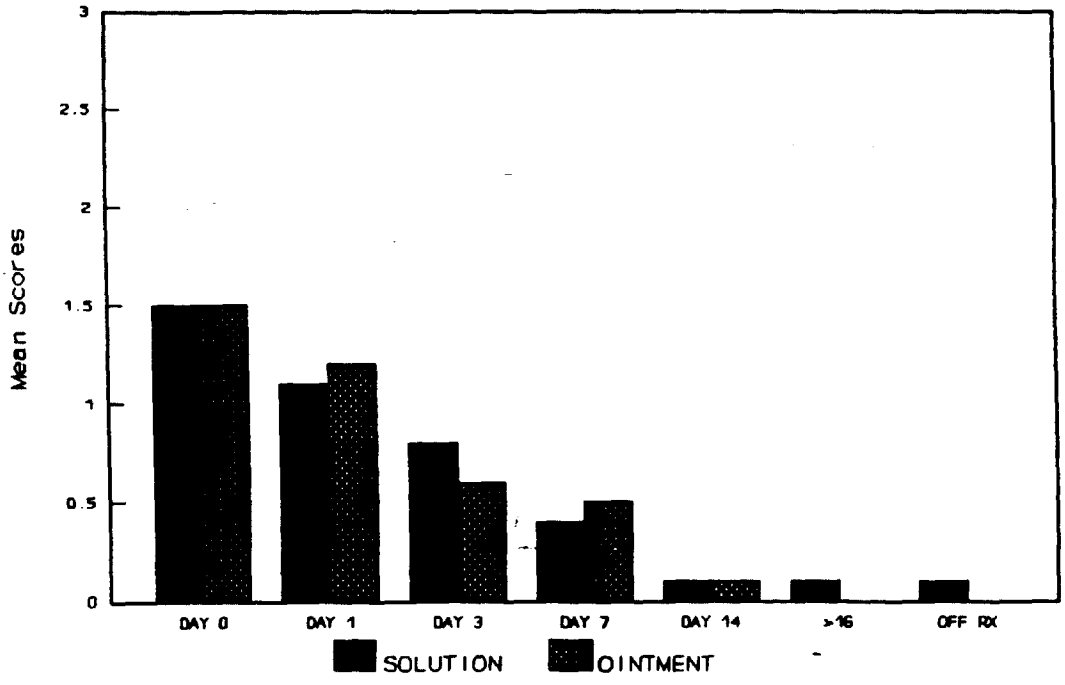

## CELLS



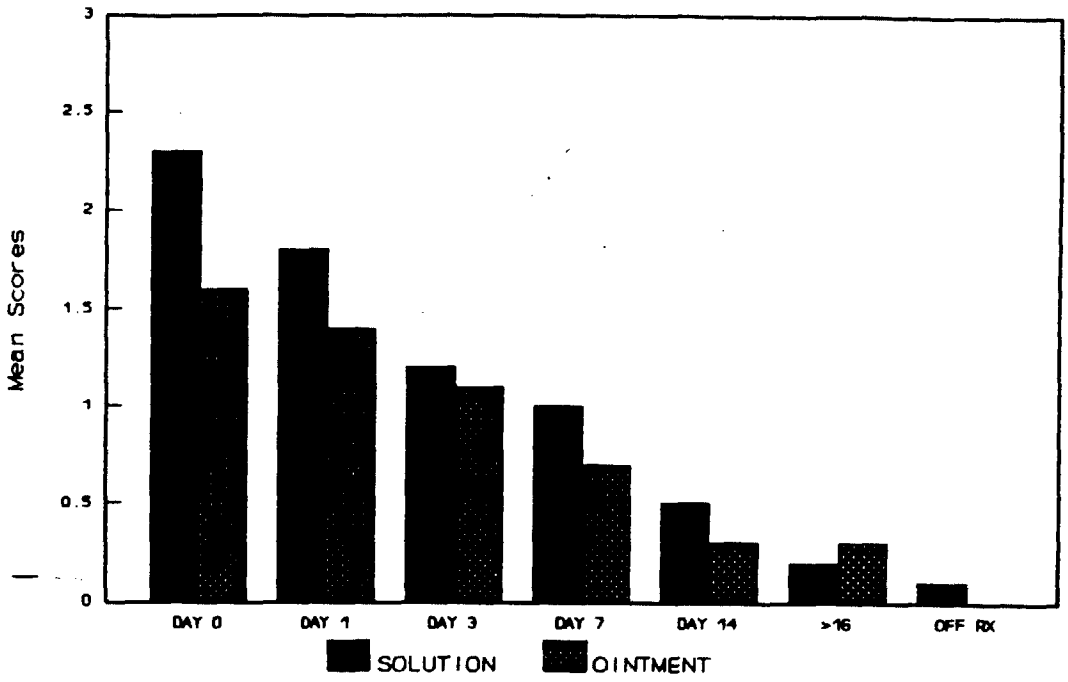
FLARE




DISCHARGE



# ERYTHEMA




APPEARS THIS WAY
ON ORIGINAL

## Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 2

The following analyses compare data for 39 Ciprofloxacin Ointment patients to 13 non-enrolled standard therapy patients from Protocol C-90-94. **All analytical results should be interpreted with some degree of caution due to the small number of standard therapy patients.**

### Patient Demographics and Day 0 Ulcer Characteristics for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 2

No significant differences were found for sex or race ($p > 0.42$) but Standard Therapy patients were significantly older ($p < 0.05$). Day 0 ulcer diameter, depth and duration were not significantly different between treatments ($p > 0.14$).

| SEX: | MALE | | FEMALE | |
|---|---|---|---|---|
| | N | % | N | % |
| Oint | 19 | 48.7 | 20 | 51.3 |
| Std Tx | 8 | 61.5 | 5 | 38.5 |

p=0.42, Chi-square test for independence

| RACE: | Caucasian | | Black | | Asian | | Other | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Oint | 32 | 82.1 | 1 | 2.6 | 1 | 2.6 | 5 | 12.8 |
| Std Tx | 11 | 84.6 | - | - | - | - | 2 | 15.4 |

p=0.87, Chi-square test for independence

| AGE: | N | MEAN | STD |
|---|---|---|---|
| Oint | 39 | 44.5 | 23.06 |
| Std Tx | 13 | 58.7 | 14.63 |

p=0.04, One-way ANOVA

| DAY 0 ULCER DIAM | < 2 mm | | 2 - 4 mm | | > 4 mm | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Oint | 17 | 43.6 | 20 | 51.3 | 2 | 5.1 |
| Std Tx | 4 | 30.8 | 6 | 46.2 | 3 | 23.1 |

p=0.18, Cochran-Mantel-Haenszel rank score test

| DAY 0 STROMAL DEPTH OF ULCER | Superficial | | Mid-Stromal | | Deep Stromal | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Oint | 19 | 48.7 | 14 | 35.9 | 6 | 15.4 |
| Std Tx | 4 | 30.8 | 7 | 53.8 | 2 | 15.4 |

p=0.38, Cochran-Mantel-Haenszel rank score test

| DURATION | N | MEAN | STD |
|---|---|---|---|
| Oint | 39 | 4.2 | 4.01 |
| Std Tx | 13 | 6.8 | 8.16 |

p=0.14, One-way ANOVA

**Comparison of Physician's Final Judgement for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 2**

| | | FINAL IMPRESSION | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TOTAL | CURED | | IMPROVED | | UNCHANGED | | WORSE | | |
| | N | N | % | N | % | N | % | N | % | p-value |
| Oint | 39 | 33 | 84.6 | 3 | 7.7 | 1 | 2.6 | 2 | 5.1 | 0.55* |
| Std Tx | 13 | 10 | 76.9 | 2 | 15.4 | - | - | 1 | 7.7 | |
| **Ulcer Diam < 2 mm** | | | | | | | | | | |
| Oint | 17 | 15 | 88.2 | - | - | - | - | 2 | 11.8 | 0.29** |
| Std Tx | 4 | 3 | 75.0 | - | - | - | - | 1 | 25.0 | |
| **Ulcer Diam 2 - 4 mm** | | | | | | | | | | |
| Oint | 20 | 17 | 85.0 | 3 | 15.0 | - | - | - | - | |
| Std Tx | 6 | 4 | 66.7 | 2 | 33.3 | - | - | - | - | |
| **Ulcer Diam > 4 mm** | | | | | | | | | | |
| Oint | 2 | 1 | 50.0 | - | - | 1 | 50.0 | - | - | |
| Std Tx | 3 | 3 | 100.0 | - | - | - | - | - | - | |

* Cochran-Mantel-Haenszel rank score test
** Cochran-Mantel-Haenszel rank score test controlling for Day 0 ulcer size

No significant treatment differences were found for physician's judgement due to the small number of patients in the Standard Therapy group ($p=0.55$). An additional analysis of physician's final judgement was performed to insure that cure rates were not dependent on ulcer size. No significant treatment differences were found after adjusting for ulcer-size due to the extremely small number of Standard Therapy patients in each ulcer diameter group ($p=0.29$).

**Comparison of Days on Treatment & Treatment Failures for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 2**

| | DAYS ON DRUG | | |
|---|---|---|---|
| | N | MEAN | STD |
| Oint | 39 | 16.8 | 8.72 |
| Std Tx | 12 | 22.0 | 8.34 |

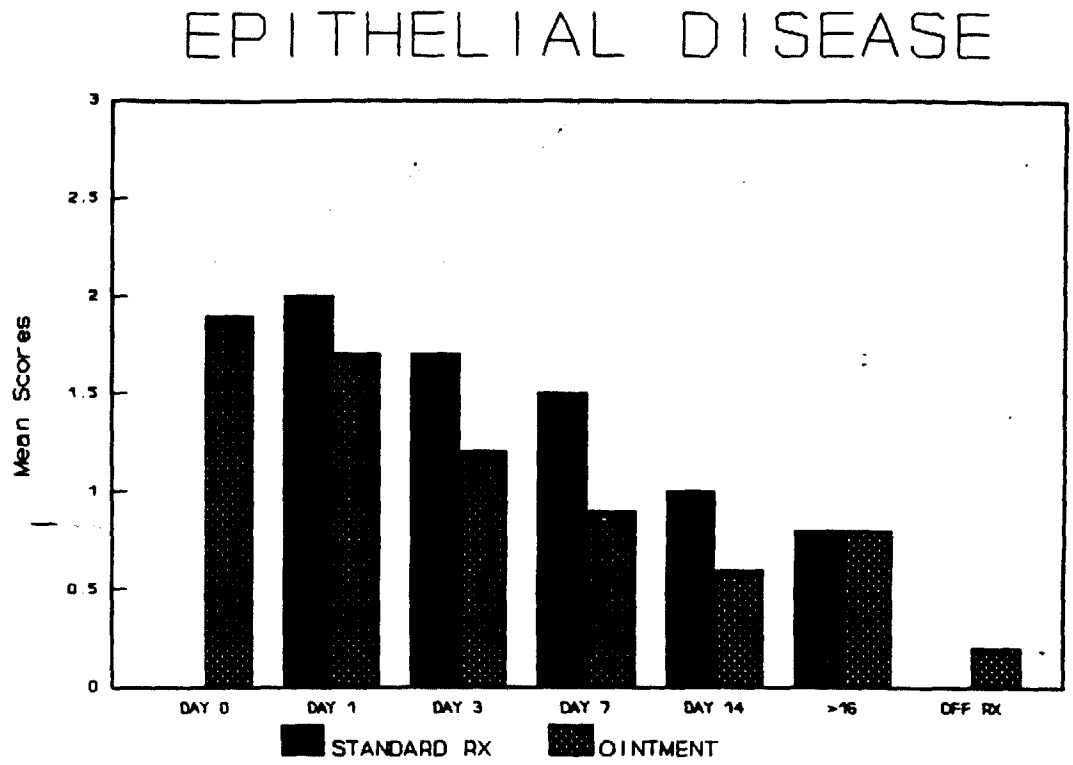
p=0.07, One-way ANOVA

| | Treatment Failed | | | |
|---|---|---|---|---|
| | No | | Yes | |
| | N | % | N | % |
| Oint | 36 | 92.3 | 3 | 7.7 |
| Std Tx | 10 | 76.9 | 3 | 23.1 |

p=0.16, Fisher's Exact test

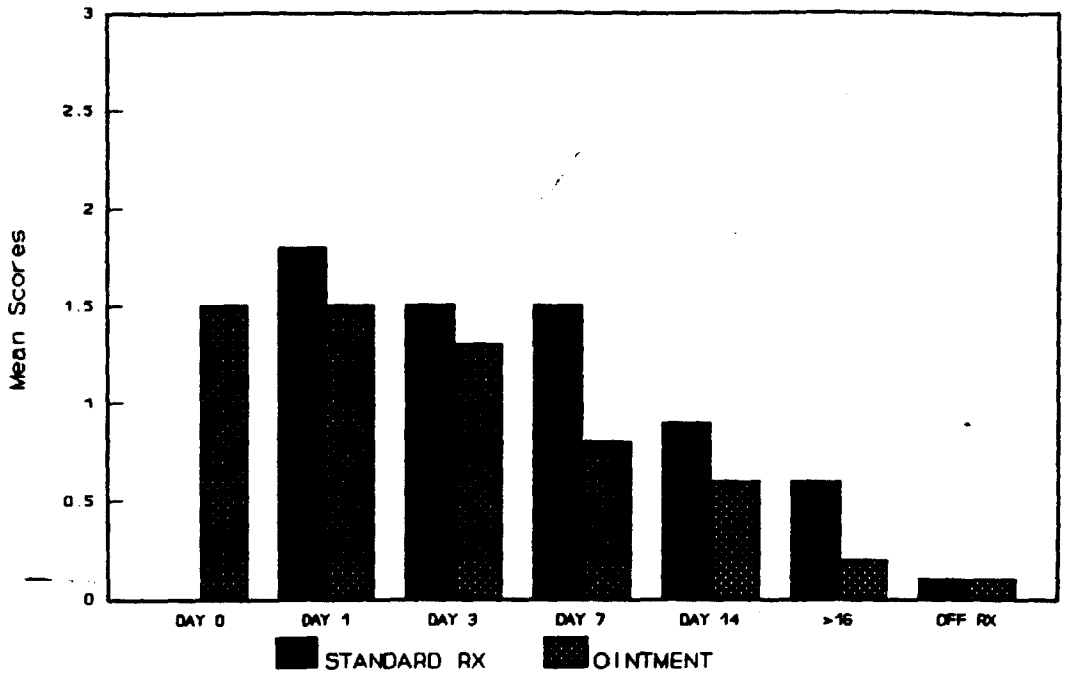
No significant treatment differences were detected for number of days on therapy of treatment failures ($p > 0.07$) due to the small number of patients in the Standard Therapy group.

**Comparison of Major Clinical Signs Associated with Corneal Ulcers for Ciprofloxacin Ointment (C-90-85) vs Standard Therapy (C-90-94) - STUDY 2**

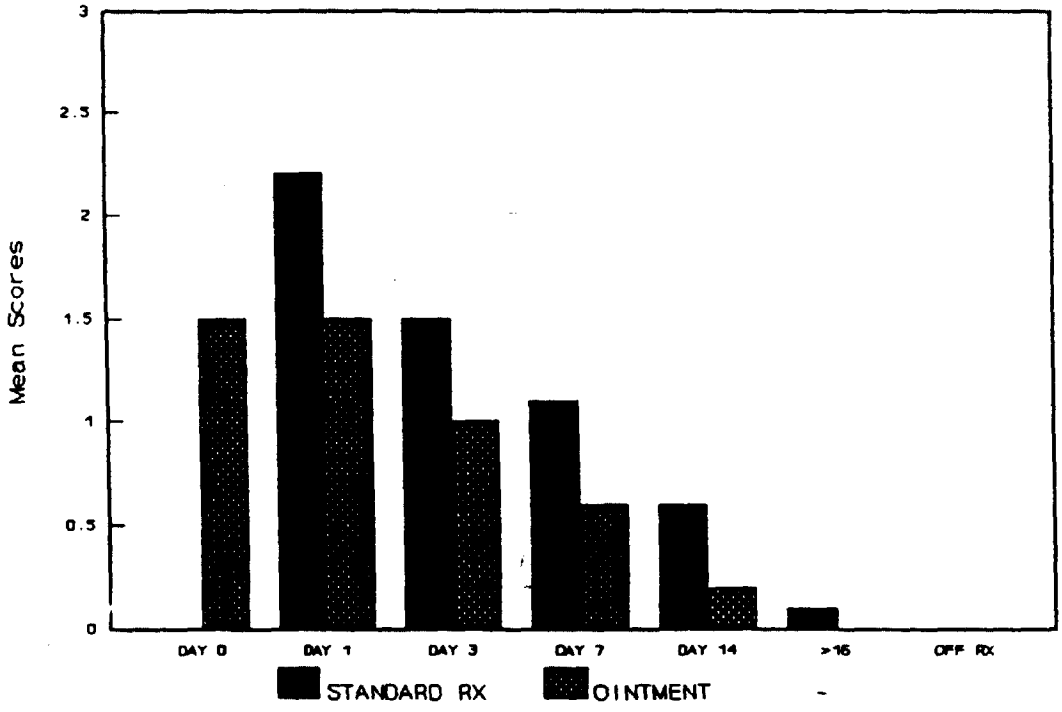



APPEARS THIS WAY
ON ORIGINAL

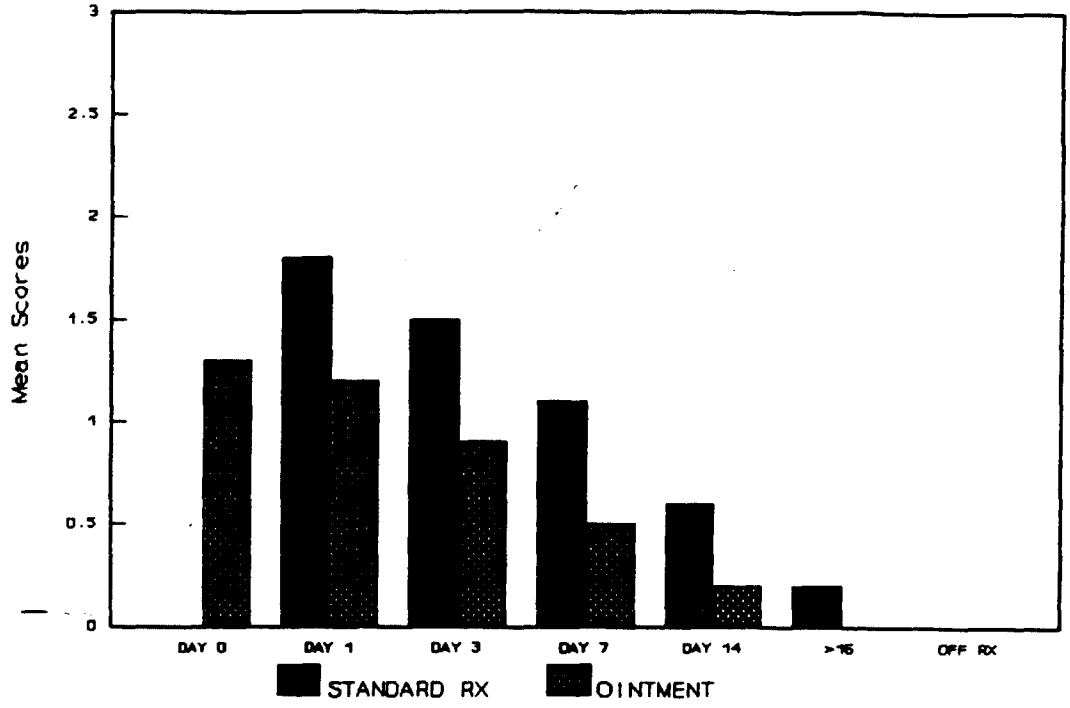
# FOCAL INFILTRATES



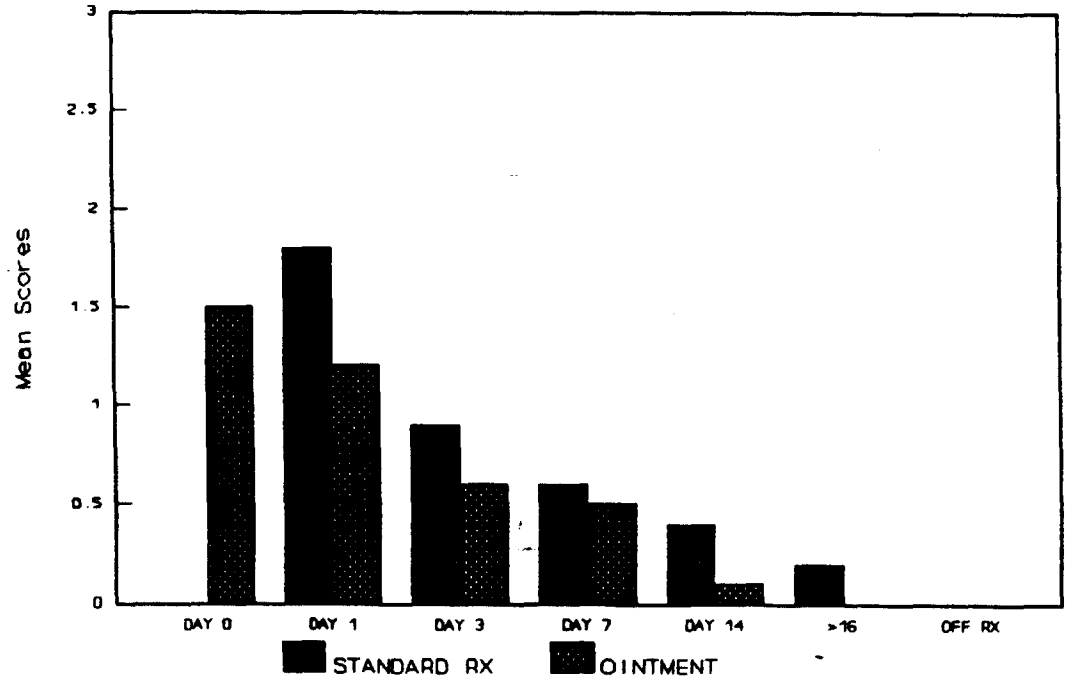

# CELLS



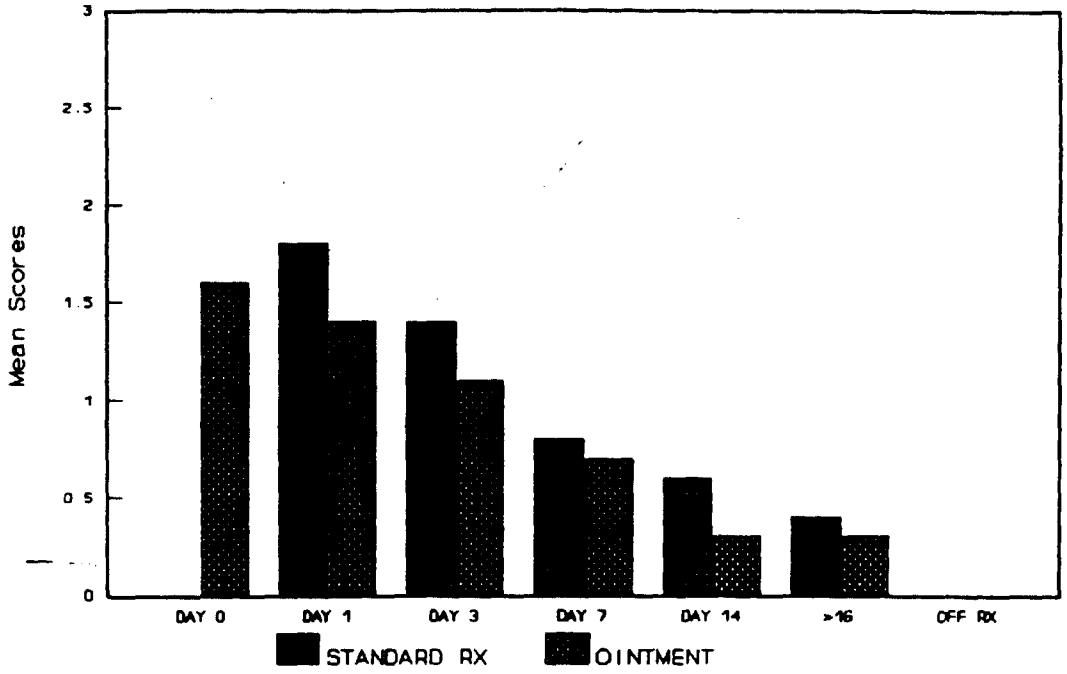
## FLARE




## DISCHARGE



# ERYTHEMA




APPEARS THIS WAY
ON ORIGINAL

## Ciprofloxacin Ointment (C-90-85) vs Historical Patients (C-90-52) - STUDY 2

The following analyses compare data for 39 Ciprofloxacin Ointment patients to 32 historical database patients who were on standard therapy (C-90-52). The historical database was based on retrospective data obtained from physician records of corneal ulcer patients who received standard therapy within one year prior to the investigator enrolling patients into the Ciprofloxacin solution study. Ocular signs and symptoms, Day 0 ulcer depth and location and demographics were not collected for historical patients.

### Day 0 Longest Ulcer Diameter (mm) for Ciprofloxacin Ointment (C-90-85) vs Historical (C-90-52) - STUDY 2

| DAY 0 ULCER DIAM | < 2 mm N | % | 2 - 4 mm N | % | > 4 mm N | % |
|---|---|---|---|---|---|---|
| Oint | 17 | 43.6 | 20 | 51.3 | 2 | 5.1 |
| Hist | 3 | 9.7 | 19 | 61.3 | 9 | 29.0 |

p<0.001, Cochran-Mantel-Haenszel rank score test

Historical standard therapy patients had significantly more ulcers > 4mm than patients on Ciprofloxacin (p<0.001).

### Comparison of Physician's Final Judgement for Ciprofloxacin Ointment (C-90-85) vs Historical (C-90-52) - STUDY 2

| | TOTAL N | FINAL IMPRESSION: CURED N | % | IMPROVED N | % | UNCHANGED N | % | WORSE N | % | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Oint | 39 | 33 | 84.6 | 3 | 7.7 | 1 | 2.6 | 2 | 5.1 | 0.31* |
| Hist | 32 | 24 | 75.0 | 3 | 9.4 | 3 | 9.4 | 2 | 6.3 | |
| **Ulcer Diam. < 2 mm** | | | | | | | | | | |
| Oint | 17 | 15 | 88.2 | . | . | . | . | 2 | 11.8 | 0.23** |
| Hist | 3 | 3 | 100.0 | . | . | . | . | . | . | |
| **Ulcer Diam. 2-4 mm** | | | | | | | | | | |
| Oint | 20 | 17 | 85.0 | 3 | 15.0 | . | . | . | . | |
| Hist | 19 | 13 | 68.4 | 2 | 10.5 | 3 | 15.8 | 1 | 5.3 | |
| **Ulcer Diam. > 4 mm** | | | | | | | | | | |
| Oint | 2 | 1 | 50.0 | . | . | 1 | 50.0 | . | . | |
| Hist | 9 | 7 | 77.8 | 1 | 11.1 | . | . | 1 | 11.1 | |

* Cochran-Mantel-Haenszel rank score test
** Cochran-Mantel-Haenszel rank score test, controlling for Day 0 Ulcer Size
Note: 1 Historical patient had a missing value for ulcer diameter

No significant treatment differences were detected for physicians judgement (p=0.31). Since the Historical study had significantly more patients with ulcer diameters larger than 4 mm, a second analysis, to adjust for differences in ulcer diameter, also indicated no significant treatment differences (p=0.23).

**Reviewer's Comments:** *There are not enough patients to adequately evaluate.*

**Comparison of Days on Treatment & Treatment Failures for Ciprofloxacin Ointment (C-90-85) vs Historical (C-90-52) - STUDY 2**

Days on Treatment

| | N | MEAN | STD | MIN | MAX |
|---|---|---|---|---|---|
| Oint | 39 | 16.8 | 8.72 | | |
| Hist | 29 | 57.8 | 52.11 | | |

p<0.001, Two-sample t-test

Treatment Failed

| | NO | | YES | |
|---|---|---|---|---|
| | N | % | N | % |
| Oint | 36 | 92.3 | 3 | 7.7 |
| Hist | 16 | 50.0 | 16 | 50.0 |

p<0.001, Chi-square test for independence

Historical standard therapy patients were on treatment significantly longer than patients on Ciprofloxacin Ointment ($p<0.001$). Historical standard therapy patients had significantly more treatment failures ($p<0.001$).

**Summary Conclusions on the treatment of Corneal Ulcers.**

Study #1

The sponsor's analysis demonstrated that Ciprofloxacin Ointment 0.3% was effective in curing 89% of the bacterial corneal ulcers and in curing or improving 94% of bacterial corneal ulcers. Statistically Ciprofloxacin Ointment 0.3% was proven to be better than Ciprofloxacin Solution, Standard Therapy and Historical Standard Therapy.

Study #2

The sponsor's analysis demonstrated that Ciprofloxacin Ointment 0.3% was effective in curing 85% of the bacterial corneal ulcers or in curing and improving 92% of bacterial corneal ulcers. Statistically it does not have enough power to rule out the possibility that Ciprofloxacin Ointment 0.3% is at least 20% less effective than Ciprofloxacin Solution and Standard Therapy.

**Reviewer's Comments:** *The analyses presented by the sponsor will need to be revised taking in consideration the patients lost to follow up and discontinued due to ADRs. The analyses also should include all the patients enrolled under protocol C-88-88 (Study 1 and 2) and not the subset used in the Ciprofloxacin Solution submission (NDA 19-992)*

**Regulatory Recommendations:**

The above clinical trials are not considered sufficient to recommend Ciprofloxacin Ointment 0.3% for approval for the indications of "treatment of bacterial conjunctivitis and bacterial corneal ulcers.

The sponsor is encouraged to amend the application with a placebo control trial for the conjunctivitis indication and a prospective randomized trial comparing Ciprofloxacin Ointment 0.3% with the already approved Ciprofloxacin 0.3% solution in the treatment of corneal ulcers.

The proposed labeling was not reviewed.

Jose A. Carreras, M.D.

cc: Orig NDA 20-369
HFD-540 Gw 5/14/94
~~HFD-520/CSO/Joyce~~
HFD-520/CHEM/Shetty
HFD-520/PHARM/Buko
HFD-520/Micro/Dionne
HFD-520/MO/Carreras
HFD-520/SMO/Chambers MAC 4/15/94

**Medical Officer's Review of NDA 20-369**
**Amendment**

| | | |
|---|---|---|
| **NDA 20-369** | **Submission date:** | 6/20/97 |
| **Amendment** | **Received date:** | 6/24/97 |
| | **Review date:** | 12/ 6/97 |

**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

Submitted: Response to Not Approvable Letter dated 5/17/94.

Related Submissions:

NDA 19-992 (Ciloxan Solution)

2 Table of Contents:



3 **Material Reviewed**
Volumes 6.1, 6.6-6.16

4 **Chemistry/Manufacturing Controls** *-See Chemistry/Manufacturing Review*
*-See Microbiology Review*

5 **Animal Pharmacology/Toxicology** *-See Pharm/Tox Review*
*-No additional issues.*

6 **Clinical Background**

6.3 **Foreign experience**
Ciloxan Ointment has also been approved in Canada, Columbia, Mexico and Uruguay. No other foreign marketing applications for the ointment formulation are pending at this time.

6.6 **Directions for Use**
The recommended dosage regimen for the treatment of conjunctivitis: apply a ½" ribbon into the conjunctival sac three times a day on the first two days, then apply a ½" ribbon two times a day for the next five days. Dosing may be extended at the discretion and instructions of the prescribing physician.

## 7 Description of Clinical Data Sources

| Review Number | Protocol Number | Indication | Control | Duration | Number of Subjects | Comments |
|---|---|---|---|---|---|---|
| 1 | C-88-23 | Clinical Pharm | None | 14 days | 40 | No control group. |
| 2 | C-93-88 | Conjunctivitis | Placebo | 3 days | 277 | Study #5 |
| 3 | C-91-29 | Conjunctivitis | Tobrex | 7 days | 203 | Study #6 |
| 4 | C-88-24 | Conjunctivitis | Tobrex | 7 days | 497 | See Review #1, Study #2. |
| 5 | C-88-94 | Conjunctivitis | Placebo | 3 days | 144 | See Review #1, Study #1. Investigator disqualified. Clinical differences not significant. |
| 6 | C-88-24 | Blepharitis | Tobrex | 7 days | 312 | No differences between Cipro and Tobrex. |
| 7 | C-90-122 | Chlamydial Conjunctivitis | None | 28 days | 24 | Pilot, No control. |
| 8 | C-88-43 | Blepharitis | Placebo | 7 days | 139 | No clinical differences between Cipro and Vehicle.. |
| 9 | C-91-22 | Blepharitis/ Conjunctivitis | Colbiocin | 7 days | 54 | Control group not recognized as effective. |
| 10 | C-91-28 | Chlamydial Conjunctivitis | Tetracycline | 21 days | 82 | Study #7 |
| 11 | C-90-85 | Keratitis | None | 14 days | 255 | See Review #1, Study #3. |
| 12 | C-90-52 | Keratitis | None | 24-53 days | 228 | See Review #1, Study #4. |

## 8 Clinical Studies

### 8.1.5 Study #5 Protocol C-93-88

Title: Evaluation of the Efficacy and Safety of Ciprofloxacin Ointment 0.3% vs Placebo for Treatment of Acute Bacterial Conjunctivitis

Objective: To determine the clinical and microbiological efficacies and safety of Ciprofloxacin Ophthalmic Ointment 0.3% versus placebo for treating acute (≤ 30 days) bacterial conjunctivitis in patients ≥2 years of age.

Study Design: Prospective, randomized, vehicle controlled, double-masked, parallel group

Dosage: Apply a ½" ribbon to the inferior palpebral conjunctiva (cul-de-sac) of the affected eye(s), three times a day while awake (approximately 9 a.m., 3 p.m., and 9 p.m.) on Days 1 and 2; then twice a day while awake (approximately 9 a.m. and 9 p.m.) On Day 3.

Inclusion Criteria:

Patients must have exhibited ocular discharge and some sticking together of the eyelids (e.g., upon awaking). A minimum score of 1 should be present for exudation/discharge and bulbar conjunctiva. Patients must exhibit a total baseline of 4 or greater of the following signs combined (exudation/discharge, bulbar conjunctival inflammation, lid erythema/swelling and palpebral conjunctiva/inflammation).

Bacterial specimens were obtained from the conjunctiva and lid margin 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

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.

Clinical observation and evaluation of signs and symptoms were performed on Days 1, 2, 3 and 4. The conjunctiva/lid margin of the affected eye(s) were cultured for bacteria on Days 1 and 4. Signs and symptoms were evaluated and recorded at each visit, as well as physician judgment.

| Activity | Day 1 Visit | Day 2 Visit | Day 3 Visit | Day 4 Visit |
|---|---|---|---|---|
| Patient Screening | X | | | |
| Informed Consent | X | | | |
| Patient History | X | | | |
| Visual Acuity | X | X | X | X |
| Ocular Signs and Symptoms Obtained | X | X | X | X |
| Bacterial Specimens Collected | X | | | X |
| Physician's Follow-up Judgment Made | | X | X | X |
| Exit Form Completed | | | | X |
| Medical Event Form Completed, If Applicable | | X | X | X |

Evaluation Terms:

| Verdict | Definition |
|---|---|
| Eradication (E) | Infection Organism originally present above threshold on Day 1 is absent in follow-up culture. |
| Reduction (R) | Pathogen originally present above threshold on Day 1 is reduced to a count below threshold in a follow-up culture. |
| Persistence (NC) | Pathogen originally present above threshold on Day 1 is reduced to a count below Day 1 count, but is above or equal to threshold in follow-up culture. |
| Proliferation (P) | Pathogen originally present above threshold on Day 1 is increased to a count above Day 1 count in follow-up culture. |

| Verdict | Definition |
|---|---|
| Cured | Absence of signs or symptoms |
| Improved | A unit change in two or more signs or symptoms |
| Unchanged | No response in overall change in signs or symptoms |
| Worse | Overall increase in signs or symptoms |

| Investigator | | Ciprofloxacin | | Vehicle | |
|---|---|---|---|---|---|
| | | Enrolled | Evaluable | Enrolled | Evaluable |
| 1770 | Bryce Barker, M.D.<br>Salt Lake City, UT 84120 | 1 | 1 | 0 | 0 |
| 1692 | Steven J. Dell, M.D.<br>Austin, TX 78746 | 18 | 10 | 18 | 11 |
| 1736 | Kenneth M. Haik, M.D.<br>New Orleans, LA 70188 | 16 | 11 | 17 | 8 |
| 1768 | Graham B. Kretchman, M.D.<br>Phoenix, AZ 85006 | 19 | 7 | 20 | 9 |
| 1735 | George M. Lowry, M.D.<br>San Antonio, TX 78209 | 23 | 6 | 22 | 11 |
| 1767 | Jane Portnoy, M.D.<br>C. Thomas Moran, M.D.<br>Louisville, KY 40205 | 17 | 12 | 17 | 10 |
| 1710 | David G. Shulman, M.D.<br>San Antonio, TX 78209 | 20 | 10 | 19 | 10 |
| 1805 | Francis J. Wapner, M.D.<br>Salt Lake City, UT 84124 | 25 | 11 | 25 | 13 |
| Total | | 139 | 68 | 138 | 72 |

**Intent to Treat Analysis**

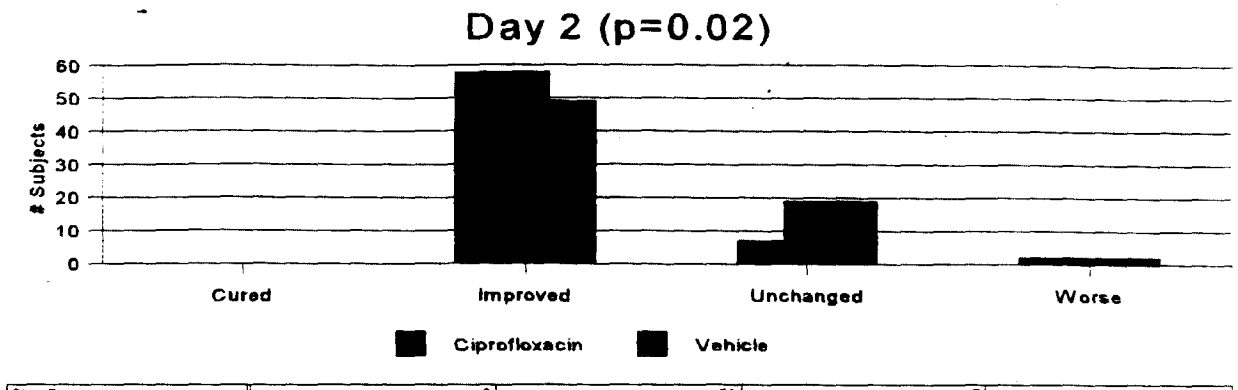
| | Treatment | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|---|
| Observed at Visit | Ciprofloxacin | 139 | 136 | 121 | 137 |
| | Vehicle | 138 | 132 | 123 | 132 |
| Discontinued | Ciprofloxacin | 0 | 0 | 2 | 2 |
| | Vehicle | 0 | 1 | 4 | 6 |
| Missed Visits | Ciprofloxacin | 0 | 3 | 16 | 0 |
| | Vehicle | 0 | 5 | 11 | 0 |

**Patients Who Did Not Complete the Study as Planned**

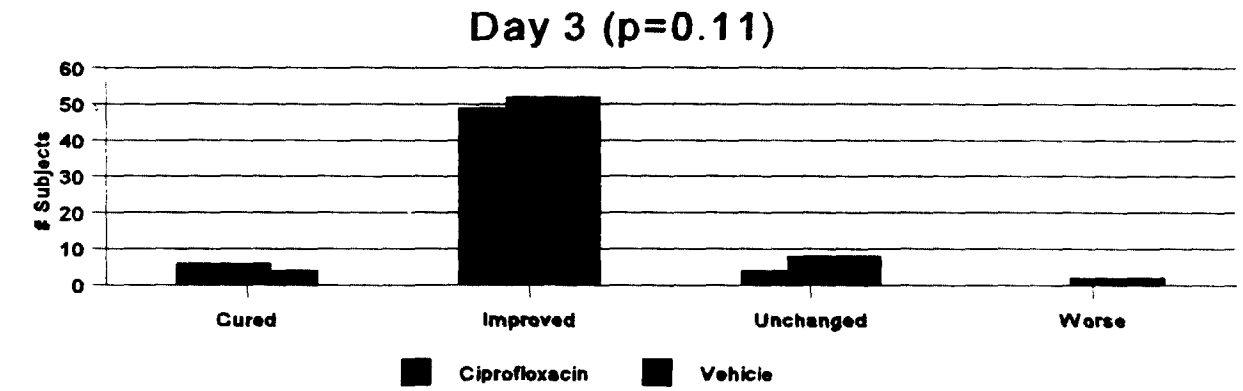
| | | | | | |
|---|---|---|---|---|---|
| 1692 | 112 | Placebo | Patient Decision | | |
| 1692 | 119 | Placebo | Lost to follow-up | | |
| 1692 | 127 | Placebo | Adverse Event - | Iritis | Day 2 |
| 1692 | 136 | Cipro | Adverse Event - | Otitis Media | Day 1 |
| 1735 | 410 | Placebo | Adverse Event - | Anxiety | Day 2 |
| 1735 | 414 | Cipro | Adverse Event - | Flu Syndrome | Day 2 |
| 1767 | 1009 | Placebo | Patient Reason | | |
| 1767 | 1017 | Placebo | Treatment Failure | | |

| **Demographics** | **Number of patients** | |
|---|---|---|
| | **Cipro** | **Vehicle** |
| **Gender** | | |
| Male | 53 | 53 |
| Female | 86 | 85 |
| **Race** | | |
| Caucasian | 106 | 98 |
| Black | 14 | 8 |
| Asian | 0 | 2 |
| Hispanic | 18 | 28 |
| American Indian | 1 | 2 |
| **Iris Color** | | |
| Brown | 68 | 64 |
| Hazel | 11 | 15 |
| Green | 22 | 16 |
| Blue | 36 | 43 |
| Grey | 2 | 0 |
| **Mean Age** | 25.5 | 27.7 |
| **Age Range** | 2-83 | 2-92 |
| **Pediatric Range** | | |
| Age 2 | 11 | 9 |
| Age 3 | 10 | 6 |
| Age 4 | 6 | 7 |
| Age 5 | 3 | 6 |
| Age 6 | 3 | 3 |
| Age 7 | 4 | 1 |
| **Mean Duration of Ocular Involvement (days)** | 5.2 | 5.6 |

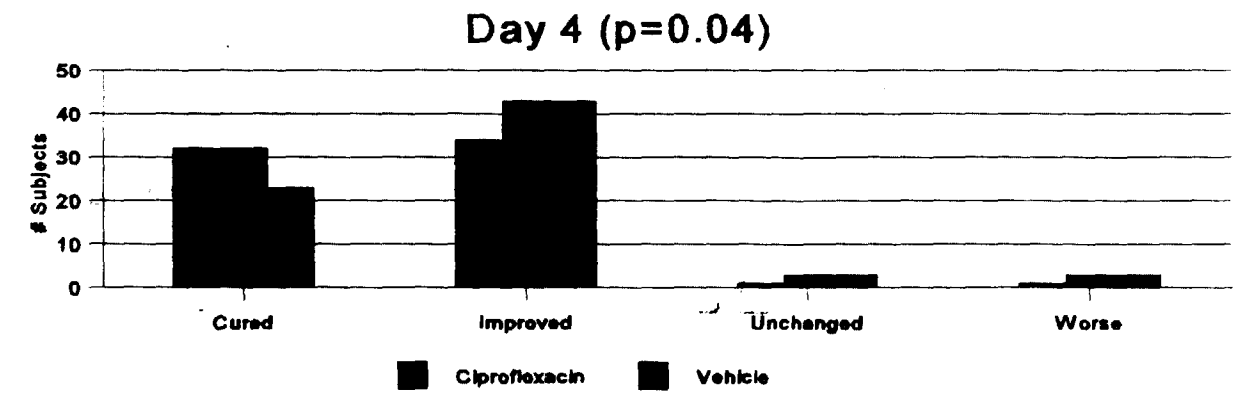
**Clinical Efficacy: Physician's Judgement - Efficacy Group (culture positive)**




| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 0 | 58 | 7 | 2 |
| Vehicle | 0 | 49 | 19 | 2 |

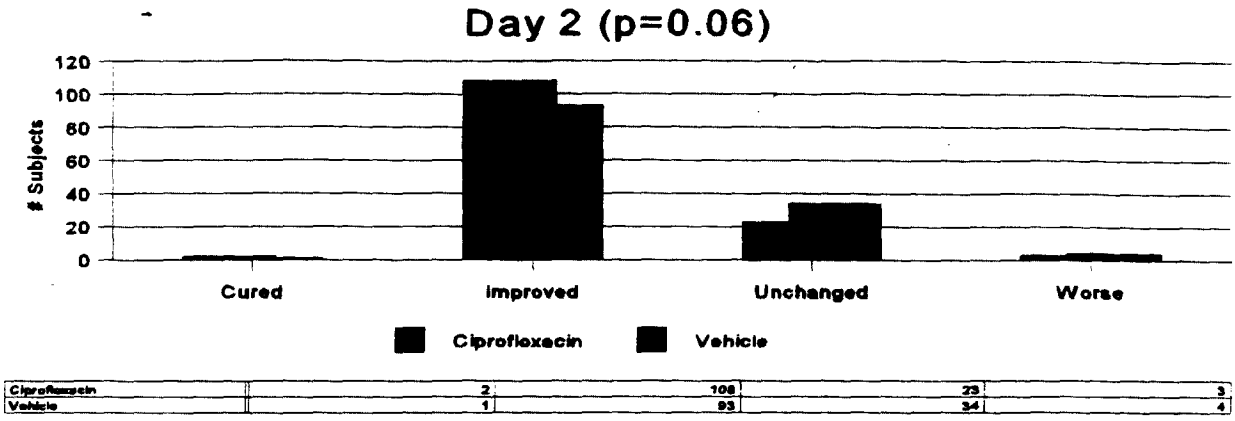



| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 6 | 49 | 4 | 0 |
| Vehicle | 4 | 52 | 8 | 2 |

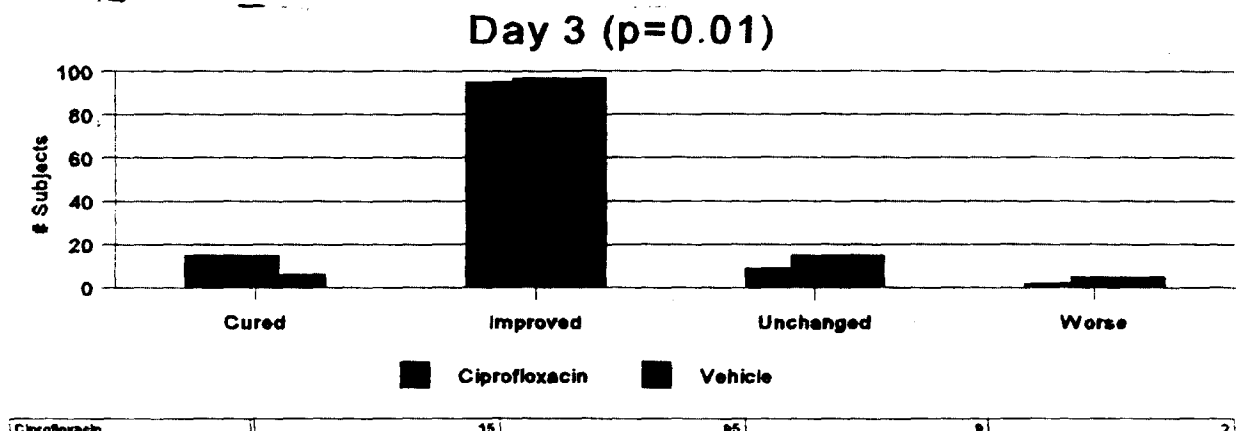



| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 32 | 34 | 1 | 1 |
| Vehicle | 23 | 43 | 3 | 3 |

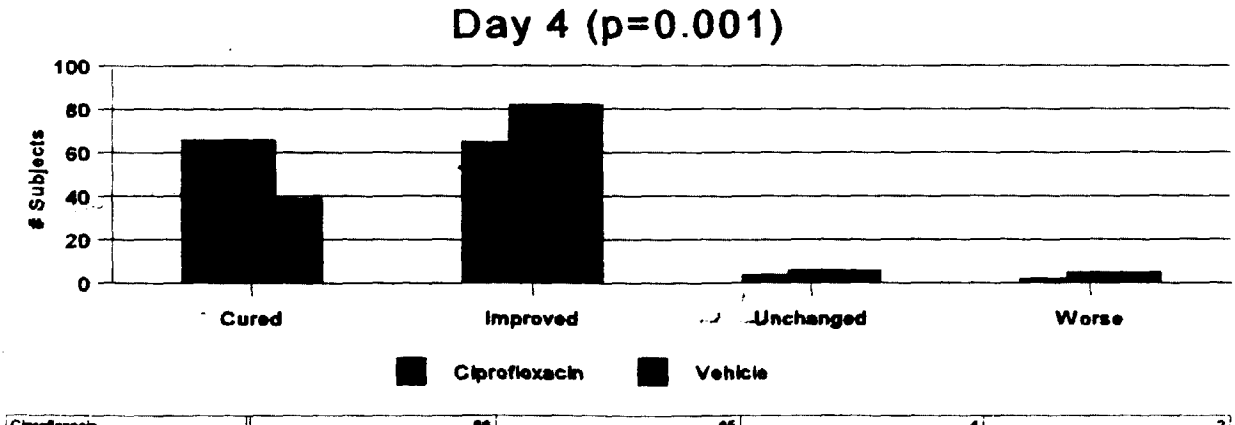
**Clinical Efficacy: Physician's Judgement Intent to Treat Group**




| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 2 | 108 | 23 | 3 |
| Vehicle | 1 | 93 | 34 | 4 |

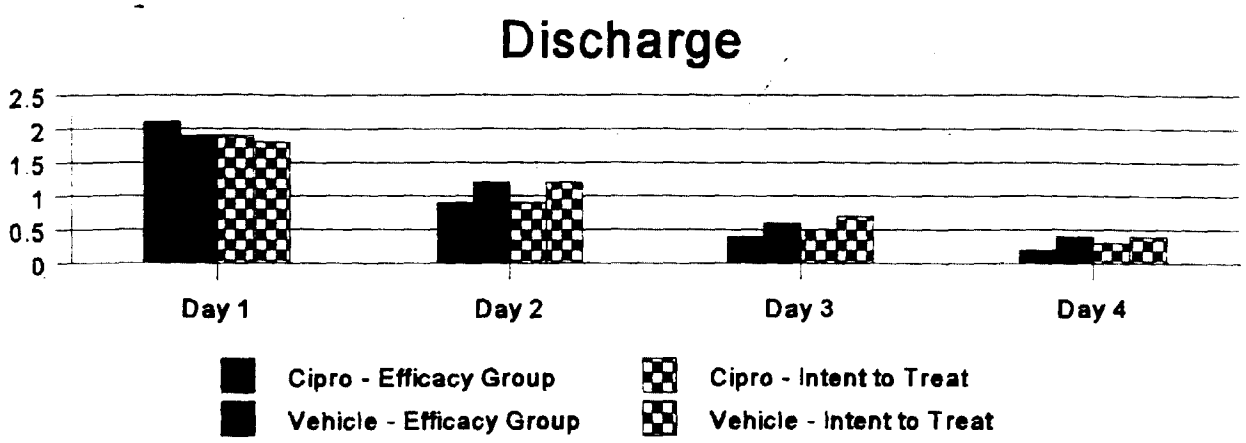



| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 15 | 95 | 9 | 2 |
| Vehicle | 6 | 97 | 15 | 5 |



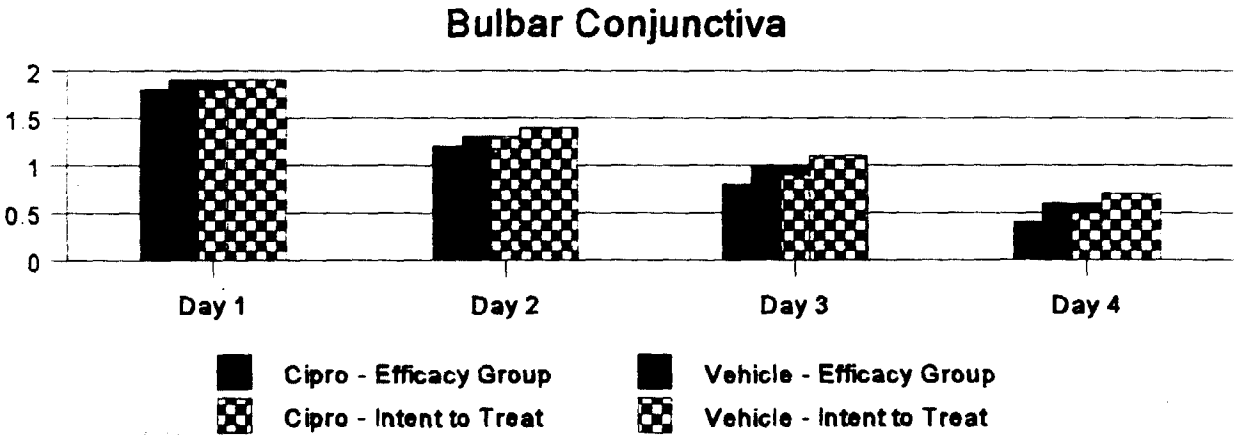

| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 66 | 95 | 4 | 2 |
| Vehicle | 39 | 82 | 9 | 5 |

Discharge



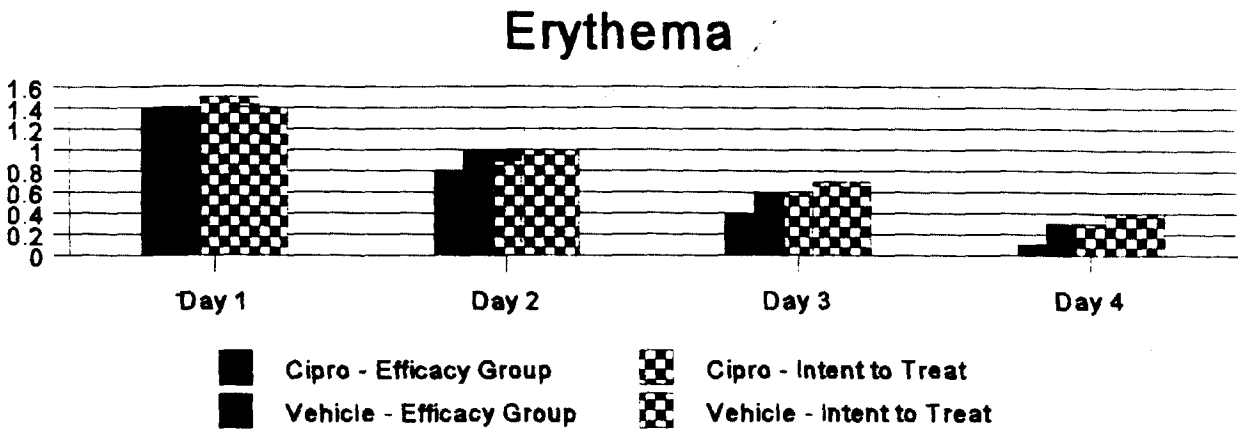

| | | | | |
|---|---|---|---|---|
| Cipro - Efficacy Group | 2.1 | 0.9 | 0.4 | 0.2 |
| Vehicle - Efficacy Group | 1.9 | 1.2 | 0.6 | 0.4 |
| Cipro - Intent to Treat | 1.9 | 0.9 | 0.5 | 0.3 |
| Vehicle - Intent to Treat | 1.8 | 1.2 | 0.7 | 0.4 |

Bulbar Conjunctiva



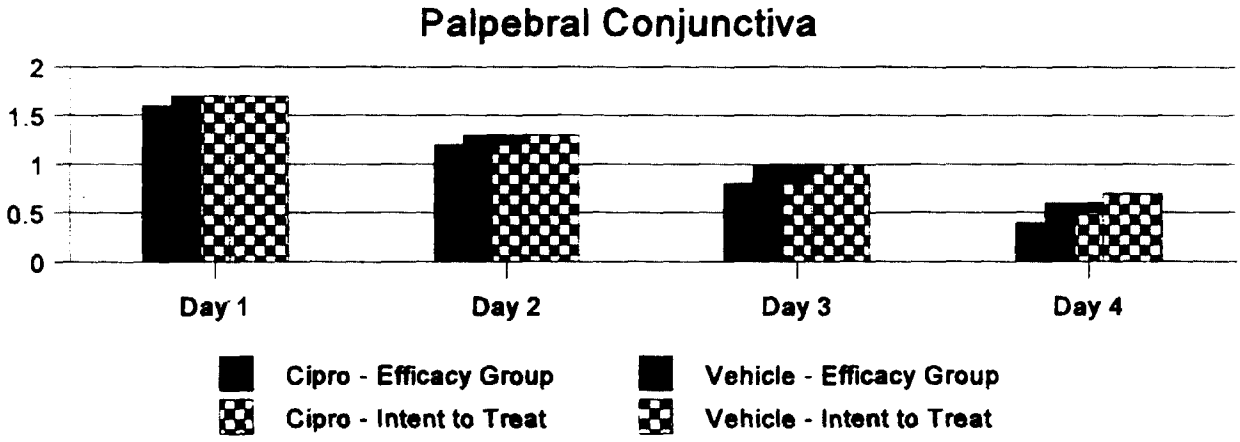

| | | | | |
|---|---|---|---|---|
| Cipro - Efficacy Group | 1.8 | 1.2 | 0.8 | 0.4 |
| Vehicle - Efficacy Group | 1.9 | 1.3 | 1 | 0.8 |
| Cipro - Intent to Treat | 1.8 | 1.3 | 0.9 | 0.5 |
| Vehicle - Intent to Treat | 1.9 | 1.4 | 1.1 | 0.7 |

Erythema



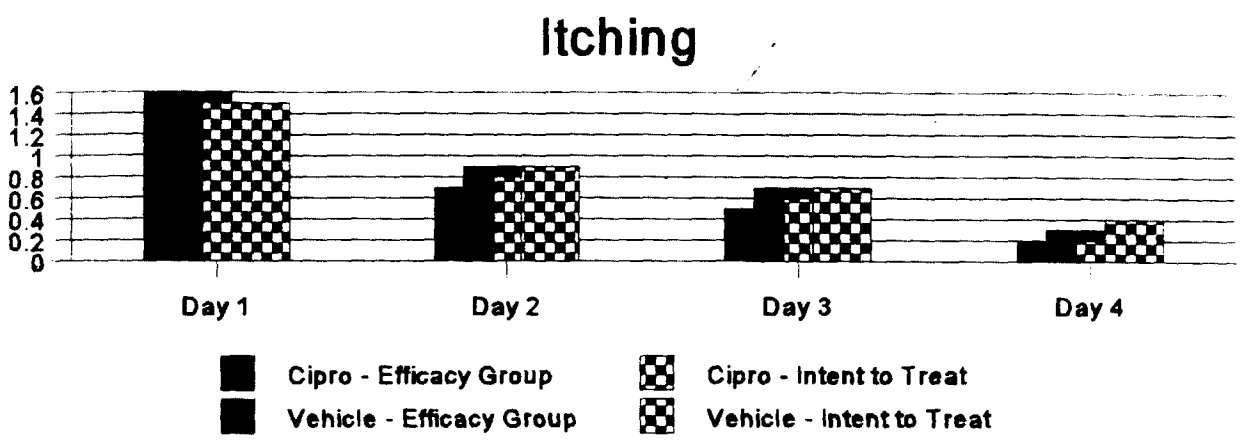

| | | | | |
|---|---|---|---|---|
| Cipro - Efficacy Group | 1.4 | 0.8 | 0.4 | 0.1 |
| Vehicle - Efficacy Group | 1.3 | 1 | 0.6 | 0.3 |
| Cipro - Intent to Treat | 1.5 | 0.9 | 0.6 | 0.3 |
| Vehicle - Intent to Treat | 1.4 | 1 | 0.7 | 0.4 |

Palpebral Conjunctiva



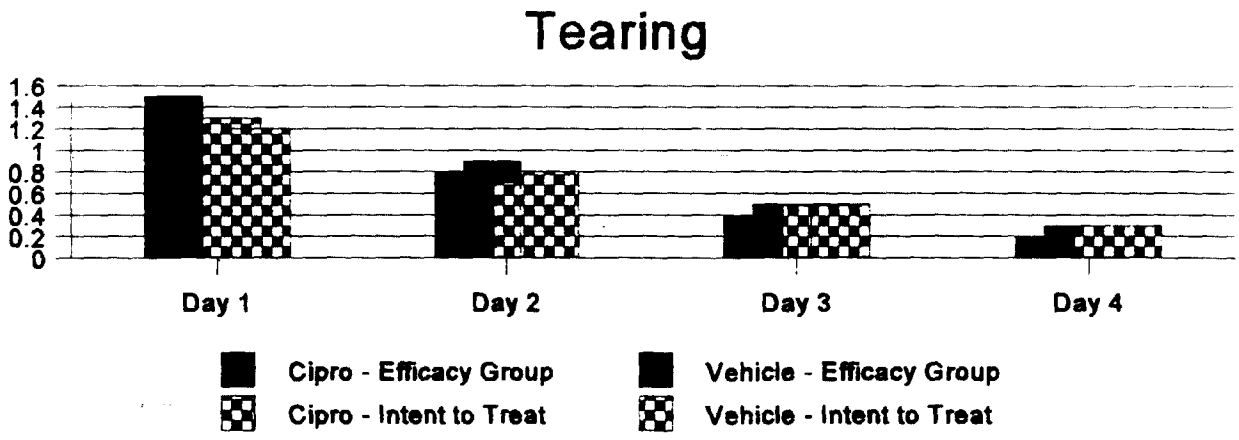

| | | | | |
|---|---|---|---|---|
| Cipro - Efficacy Group | 1.6 | 1.2 | 0.8 | 0.4 |
| Vehicle - Efficacy Group | 1.7 | 1.3 | 1 | 0.6 |
| Cipro - Intent to Treat | 1.7 | 1.2 | 0.8 | 0.5 |
| Vehicle - Intent to Treat | 1.7 | 1.3 | 1 | 0.7 |

Itching




| | | | | |
|---|---|---|---|---|
| Cipro - Efficacy Group | 1.6 | 0.7 | 0.5 | 0.2 |
| Vehicle - Efficacy Group | 1.6 | 0.9 | 0.7 | 0.3 |
| Cipro - Intent to Treat | 1.5 | 0.8 | 0.6 | 0.2 |
| Vehicle - Intent to Treat | 1.5 | 0.9 | 0.7 | 0.4 |

Tearing




| | | | | |
|---|---|---|---|---|
| Cipro - Efficacy Group | 1.5 | 0.8 | 0.4 | 0.2 |
| Vehicle - Efficacy Group | 1.3 | 0.9 | 0.5 | 0.3 |
| Cipro - Intent to Treat | 1.3 | 0.7 | 0.5 | 0.3 |
| Vehicle - Intent to Treat | 1.2 | 0.8 | 0.5 | 0.3 |

Statistical Significance of Cardinal Signs

| | Efficacy Group | | | | Intent to Treat Group | | | |
|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | Day 4 | Day 1 | Day 2 | Day 3 | Day 4 |
| Discharge | .19 | **.04** | .35 | **.02** | .44 | **.03** | .20 | **.05** |
| Bulbar Conjunctiva | .63 | .36 | .10 | .06 | .30 | .28 | **.04** | **.02** |
| Erythema | .46 | .17 | .13 | **.01** | .32 | .24 | .22 | **.01** |
| Palpebral Conjunctiva | .41 | .31 | **.04** | .20 | .49 | .29 | **.02** | **.02** |

**Reviewer's Comments:** *All differences favored Ciprofloxacin Ointment.*

## Microbiological

**Antibacterial Treatment Efficacies by Organism (Day 4)**

| | Ciprofloxacin Ophthalmic Ointment | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (n) | E | R | NC | P | (n) | E | R | NC | P |
| Gram-Positive | | | | | | | | | | |
| *Staphylococcus aureus* | 14 | 12 | 2 | | | 11 | 4 | 2 | 1 | 4 |
| *Staphylococcus epidermidis* | 11 | 6 | 4 | | 1 | 11 | 4 | 6 | | 1 |
| *Staphylococcus*, coag. neg. | 1 | 1 | | | | 1 | | 1 | | |
| *Micrococcus* spp. | 1 | 1 | | | | 0 | | | | |
| *Streptococcus pneumoniae*[b] | 27 | 16 | | 9 | 2 | 37 | 15 | | 9 | 13 |
| *Streptococcus pyogenes* | 0 | | | | | 1 | | | 1 | |
| *Enterococcus* sp. | 1 | 1 | | | | 0 | | | | |
| *Streptococcus* spp. | 6 | 6 | | | | 6 | 6 | | | |
| *Corynebacterium* spp. | 6 | 6 | | | | 5 | 3 | 2 | | |
| Gram-Negative | | | | | | | | | | |
| *Haemophilus influenzae* | 16 | 15 | | 1 | | 13 | 7 | | 5 | 1 |
| *Haemophilus parainfluenzae* | 0 | | | | | 1 | 1 | | | |
| *Moraxella catarrhalis* | 1 | 1 | | | | 0 | | | | |
| *Acinetobacter* spp. | 1 | 1 | | | | 1 | | | 1 | |
| *Neisseria* spp. | 1 | 1 | | | | 2 | 1 | | 1 | |
| *Pseudomonas* spp. | 1 | 1 | | | | 0 | | | | |
| *Enterobacteriaceae* spp.[c] | 2 | 1 | | 1 | | 1 | 1 | | | |
| Grand Total[b] | 89 | 69 | 6 | 11 | 3 | 90 | 42 | 11 | 18 | 19 |
| (%) | | (78) | (7) | (12) | (3) | | (47) | (12) | (20) | (21) |

[a]Key: n = Total number of isolates per patient (worst case verdict) for each treatment group (see Appendix C)
E = Eradication R = Reduction NC = Persistence P = Proliferation

[b]p=0.04; Cochran-Mantel-Haenszel Rank Score Test

[c]*Enterobacteriaceae* spp. = Species include: *E. coli* (E3); *Proteus* spp. (E5); or *S. marcescens* (E6)

NOTE: Percents may not add to 100% due to rounding.

**Adverse Experiences**

| | Ciprofloxacin (N=139) | Vehicle (N=138) |
|---|---|---|
| Keratopathy | 6 | 7 |
| Decreased Visual Acuity | 2 | 0 |
| Fever | 2 | 2 |
| Blurred Vision | 1 | 1 |
| Chalazion | 1 | 0 |
| Discomfort | 1 | 0 |
| Flu Syndrome | 1 | 0 |
| Foreign Body Sensation | 1 | 0 |
| Lymphadenopathy | 1 | 3 |
| Otitis Media | 1 | 0 |
| Vomiting | 1 | 0 |
| Accidental Injury | 0 | 1 |
| Anxiety | 0 | 1 |
| Increased Cough | 0 | 1 |
| Iritis | 0 | 1 |
| Joint Disorder | 0 | 1 |
| Lid Ulcer | 0 | 1 |
| Nausea | 0 | 1 |
| Urticaria | 0 | 1 |

**Reviewer's Comments:** *The majority of the events listed are likely to be related to the initial conjunctivitis.*

**Study #5 Summary:**

1. Ciprofloxacin Ointment was superior to its vehicle with respect to the physician's judgement and microbiological eradication.

2. The reported adverse experiences are lower than expected since it is known that blurring will occur with all ophthalmic ointments, yet it is rarely reported in this study.

## 8.6 Study #6 Protocol C-91-29

Title: Efficacy and Safety of Ciprofloxacin Ophthalmic Ointment vs Tobrex Ophthalmic Ointment for Treating Bacterial Conjunctivitis in Children.

Objective: To evaluate the efficacy and safety of Ciprofloxacin Ophthalmic Ointment versus TOBREX® Ophthalmic Ointment in Children

Study Design: Prospective, randomized, vehicle controlled, double-masked, parallel group

Dosage: Apply a ½" ribbon to the inferior palpebral conjunctiva (cul-de-sac) of the affected eye(s), three times a day while awake (approximately 9 a.m., 3 p.m., and 9 p.m.) on Days 1 and 2; then twice a day while awake (approximately 9 a.m. and 9 p.m.) On Days 3-7.

Inclusion Criteria:

Patients must have exhibited ocular discharge and some sticking together of the eyelids (e.g., upon awaking). 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 the same as Study #5.

Clinical observation and evaluation of signs and symptoms were performed on Days 0, 3 and 7. The conjunctiva/lid margin of the affected eye(s) were cultured for bacteria on Days 0 and 7. Signs, symptoms and physician's judgement were evaluated each visit.

| Activity | Day 0 | Day 3 (±2) | Day 7 (±2) |
|---|---|---|---|
| Patient Screening | X | | |
| Informed Consent | X | | |
| Patient History | X | | |
| Visual Acuity | X | X | X |
| Ocular Signs and Symptoms | X | X | X |
| Bacterial Specimens Collected | X | | X |
| Physician's Follow-up Judgment Made | | X | X |
| Exit Form Completed | | | X |
| Medical Event Form Completed | | X | X |

Evaluation Terms: *Same as Study #5*

| Investigator | | Ciprofloxacin | | Tobramycin | |
|---|---|---|---|---|---|
| | | Enrolled | Evaluable | Enrolled | Evaluable |
| 1238 | Stephen V. Scoper, MD<br>Charlottesville, VA | 8 | 3 | 9 | 5 |
| 1435 | Lee R. Hunter, MD<br>Sarasota, FL 34239 | 0 | 0 | 2 | 2 |
| 1408 | Mark S. Ruttum, MD<br>Milwaukee, WI 53226 | 2 | 1 | 2 | 2 |
| 826 | Steven Jay Lichtenstein, MD<br>Louisville, KY 40202 | 21 | 12 | 21 | 8 |
| *1688 | Mark M. Blatter, MD<br>Pittsburgh, PA 15241 | 14 | 9 | 14 | 8 |
| *1683 | Alan N. Lindsay, MD<br>Salt Lake City, UT 84102 | 16 | 12 | 16 | 12 |
| *1701 | Edward Rothstein, MD<br>Sellersville, PA 18960 | 14 | 6 | 15 | 10 |
| *1684 | Jed B. VanDenBerghe, MD<br>Salt Lake City, UT 84117 | 12 | 9 | 12 | 11 |
| *1689 | Dan Craig Henry, MD<br>Salt Lake City, UT 84117 | 16 | 13 | 16 | 14 |
| Total | | 103 | 65 | 107 | 72 |

* These individuals did not have ophthalmic training. The protocol was modified to delete gradings for palpebral conjunctiva, limbus, epithelial disease, focal stromal infiltrates, cell and flare. Grading of lid erythema, swelling, discharge and bulbar conjunctiva were performed with a pen or flash light.

**Reviewer's Comments:** *The failure to use trained individuals significantly detracts from the utility of this study to establish safety and efficacy of the proposed drug product.*

**Intent to Treat Analysis**

| | Treatment | Day 0 | Day 3 | Day 7 |
|---|---|---|---|---|
| Observed at Visit | Ciprofloxacin | 103 | 100 | 98 |
| | Tobramycin | 107 | 104 | 101 |
| Discontinued | Ciprofloxacin | 0 | 1 | 5 |
| | Vehicle | 0 | 2 | 6 |
| Missed Visits | Ciprofloxacin | 0 | 2 | 0 |
| | Vehicle | 0 | 1 | 0 |

**Patients Who Did Not Complete the Study as Planned**

| INV | PAT | TREATMENT | REASON |
|---|---|---|---|
| 826 | 705 | CIPRO | Infection - same pt as 706 |
| 1688 | 2216 | TOBREX | Otitis Media |
| 826 | 706 | TOBREX | Infection - same pt as 705 |
| 1684 | 2512 | TOBREX | Otitis Media |
| 826 | 736 | TOBREX | Lost to Follow-up |
| 1238 | 1711 | CIPRO | Lost to Follow-up |
| 1238 | 1715 | CIPRO | Lost to Follow-up |
| 1683 | 2429 | TOBREX | Personal reasons |
| 1684 | 2503 | CIPRO | Personal reasons |
| 826 | 701 | TOBREX | Culture Negative |
| 826 | 702 | CIPRO | Culture Negative |
| 826 | 703 | CIPRO | Culture Negative |
| 826 | 707 | CIPRO | Culture Negative |
| 826 | 709 | CIPRO | Culture Negative |
| 826 | 710 | TOBREX | Culture Negative |
| 826 | 713 | TOBREX | Culture Negative |
| 826 | 715 | CIPRO | Culture Negative |
| 826 | 718 | TOBREX | Culture Negative |
| 826 | 719 | CIPRO | Culture Negative |
| 826 | 722 | TOBREX | Culture Negative |
| 826 | 728 | CIPRO | Culture Negative |
| 826 | 740 | TOBREX | Culture Negative |
| 826 | 742 | TOBREX | Culture Negative |
| 1238 | 1701 | CIPRO | Culture Negative |
| 1238 | 1704 | CIPRO | Culture Negative |
| 1238 | 1705 | TOBREX | Culture Negative |
| 1238 | 1707 | CIPRO | Culture Negative |
| 1238 | 1714 | TOBREX | Culture Negative |
| 1238 | 1716 | TOBREX | Culture Negative |
| 1408 | 501 | CIPRO | Culture Negative |
| 1683 | 2403 | CIPRO | Culture Negative |

| INV | PAT | TREATMENT | REASON |
|---|---|---|---|
| 1683 | 2424 | CIPRO | Culture Negative |
| 1683 | 2426 | TOBREX | Culture Negative |
| 1683 | 2428 | CIPRO | Culture Negative |
| 1683 | 2431 | CIPRO | Culture Negative |
| 1683 | 2432 | TOBREX | Culture Negative |
| 1684 | 2506 | CIPRO | Culture Negative |
| 1684 | 2522 | TOBREX | Culture Negative |
| 1688 | 2201 | TOBREX | Culture Negative |
| 1688 | 2202 | CIPRO | Culture Negative |
| 1688 | 2204 | TOBREX | Culture Negative |
| 1688 | 2208 | CIPRO | Culture Negative |
| 1688 | 2209 | CIPRO | Culture Negative |
| 1688 | 2212 | CIPRO | Culture Negative |
| 1688 | 2227 | TOBREX | Culture Negative |
| 1689 | 2301 | CIPRO | Culture Negative |
| 1689 | 2306 | CIPRO | Culture Negative |
| 1689 | 2308 | TOBREX | Culture Negative |
| 1689 | 2311 | TOBREX | Culture Negative |
| 1689 | 2323 | CIPRO | Culture Negative |
| 1701 | 2101 | CIPRO | Culture Negative |
| 1701 | 2111 | TOBREX | Culture Negative |
| 1701 | 2116 | CIPRO | Culture Negative |
| 1701 | 2118 | CIPRO | Culture Negative |
| 1701 | 2119 | TOBREX | Culture Negative |
| 1701 | 2120 | CIPRO | Culture Negative |
| 1701 | 2122 | CIPRO | Culture Negative |
| 1701 | 2123 | CIPRO | Culture Negative |
| 1701 | 2127 | CIPRO | Culture Negative |
| 826 | 716 | TOBREX | Invalid Culture |
| 826 | 732 | TOBREX | Invalid Culture |
| 1238 | 1703 | TOBREX | Invalid Culture |
| 1684 | 2523 | CIPRO | Invalid Culture |
| 1688 | 2210 | TOBREX | Invalid Culture |
| 1688 | 2217 | TOBREX | Invalid Culture |
| 1688 | 2219 | CIPRO | Invalid Culture |
| 1701 | 2107 | CIPRO | Negative culture - OD, Invalid Culture -OS |
| 1701 | 2113 | TOBREX | Taking antibiotic for Otitis Media |
| 1701 | 2115 | TOBREX | Taking antibiotic for Otitis Media |
| 1683 | 2419 | CIPRO | **Reason not stated** |
| 1683 | 2427 | TOBREX | **Reason not stated** |
| 1684 | 2511 | TOBREX | **Reason not stated** |

**Reviewer's Comments:** *The reason why patients 2419, 2427 and 2511 did not complete the study should be provided.*

| **Demographics** | Number of patients | |
|---|---|---|
| | Cipro | Tobrex |
| Gender | | |
| Male | 58 | 58 |
| Female | 45 | 49 |
| Race | | |
| Caucasian | 92 | 96 |
| Black | 8 | 9 |
| Asian | 1 | 1 |
| Hispanic | 1 | 3 |
| Mixed | 1 | 1 |
| Mean Age | 4.5 | 4.6 |
| Age Range | 1-12 | 0-13 |
| Mean Duration of Ocular Involvement (days) | 2.4 | 1.9 |

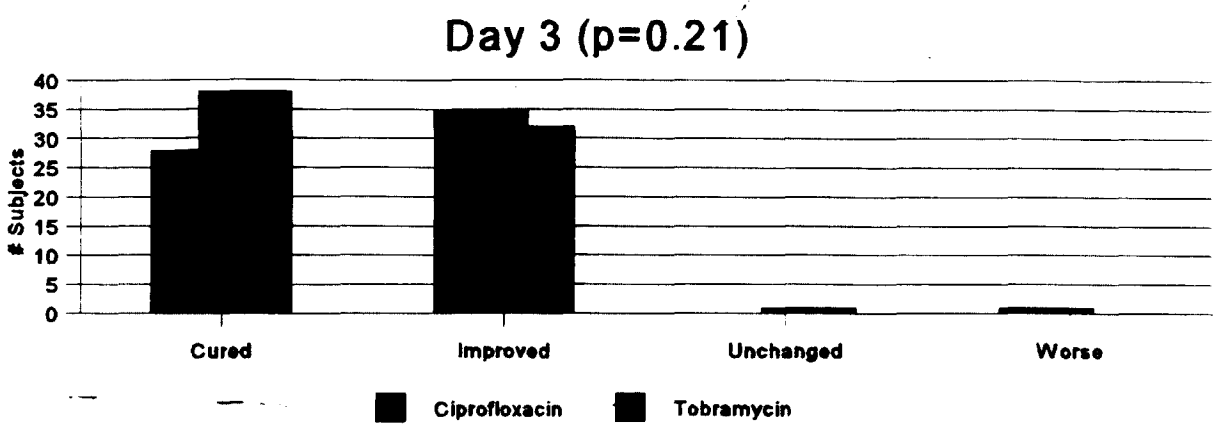
Baseline Cardinal Sign Scores for the Intent to Treat Group by Type of Investigator

| Sign | | CIPRO | | | TOBREX | | | CMH | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | MEAN | STD | N | MEAN | STD | statistic* | p-value* |
| CONJ-Bulb | Oph | 43 | 1.558 | 0.548 | 46 | 1.783 | 0.554 | 4.92 | 0.03 |
| | Non-oph | 60 | 1.400 | 0.741 | 61 | 1.557 | 0.620 | | |
| DISCHARGE | Oph | 43 | 1.884 | 0.662 | 46 | 2.065 | 0.533 | 1.52 | 0.22 |
| | Non-oph | 60 | 1.600 | 0.616 | 61 | 1.672 | 0.651 | | |
| ERYTHEMA | Oph | 43 | 1.442 | 0.700 | 46 | 1.609 | 0.614 | 8.36 | <.01 |
| | Non-oph | 60 | 1.117 | 0.804 | 61 | 1.459 | 0.743 | | |

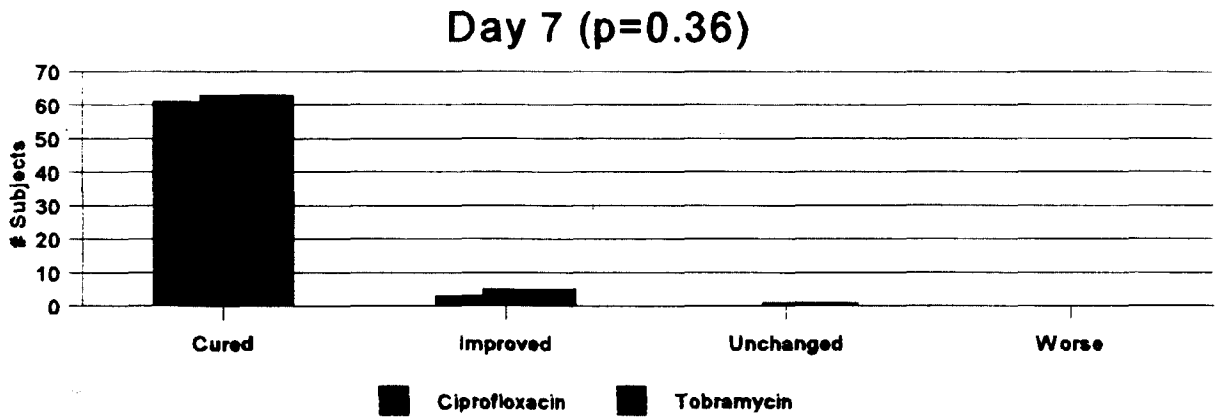
* Cochran Mantel Haenszel Rank Score Test, controlling for Type of Investigator (df=1)

**Reviewer's Comments:** *The baseline signs were not equivalent between groups. In addition, there appear to be significant differences between ophthalmologist's evaluations and non-ophthalmologist's evaluations. Where these differences exist, they should be specifically identified.*

**Clinical Efficacy: Physician's Judgement - Efficacy Group (culture positive)**

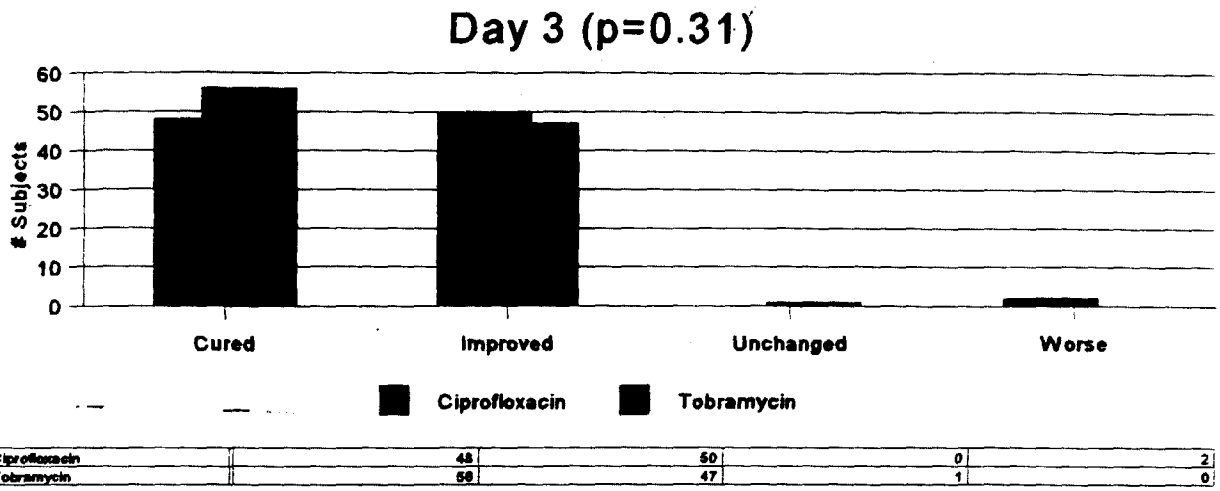



| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 28 | 35 | 0 | 1 |
| Tobramycin | 38 | 32 | 1 | 0 |

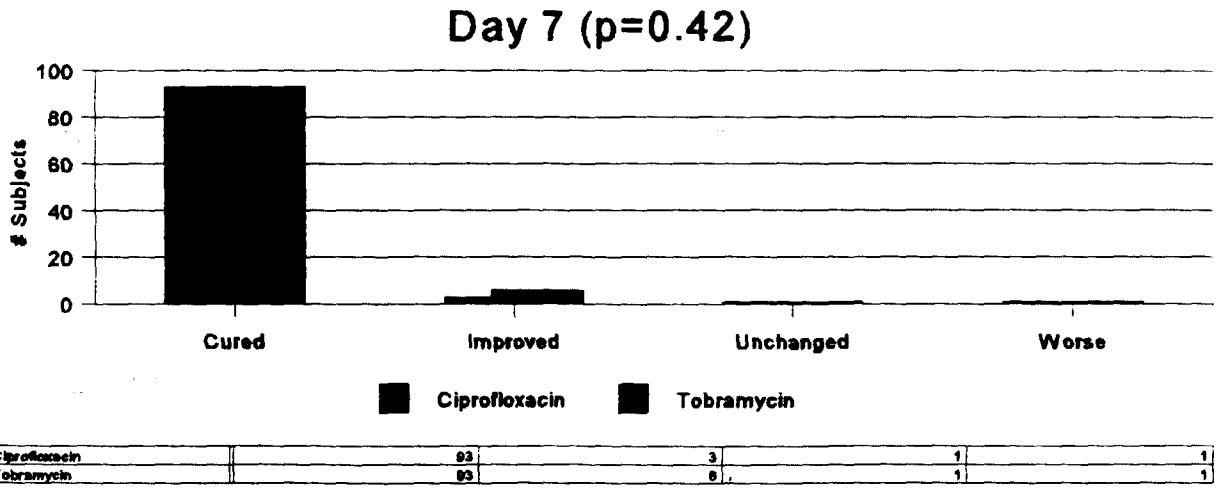



| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 61 | 3 | 0 | 0 |
| Tobramycin | 63 | 5 | 1 | 0 |

**Clinical Efficacy: Physician's Judgement Intent to Treat Group**

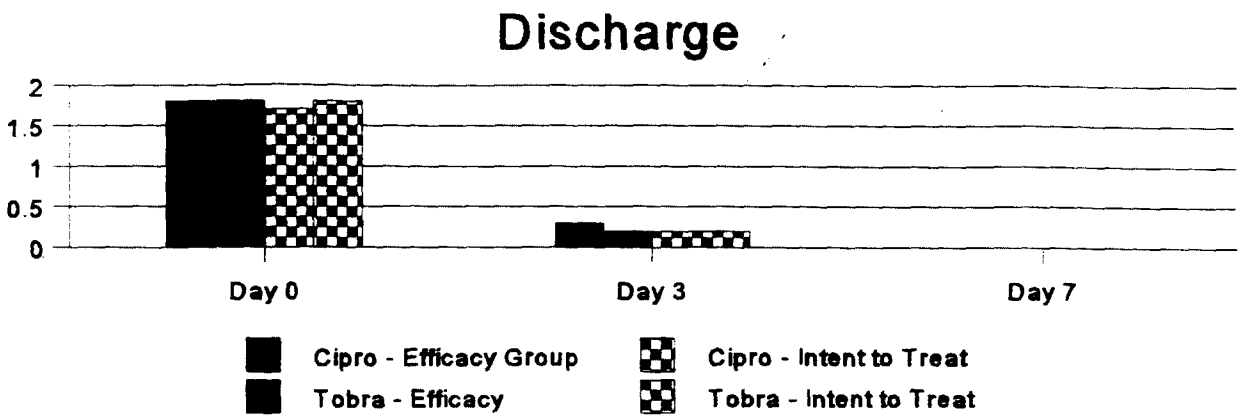



| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 48 | 50 | 0 | 2 |
| Tobramycin | 58 | 47 | 1 | 0 |



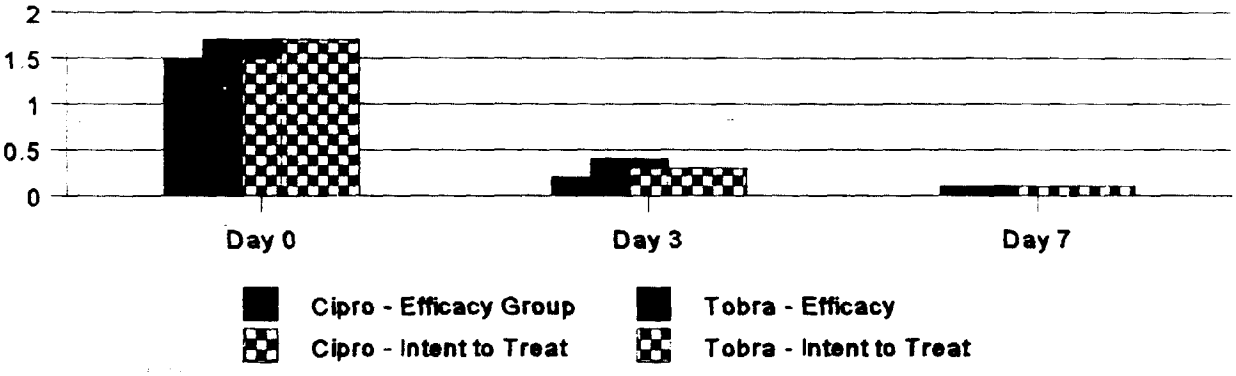

| | | | | |
|---|---|---|---|---|
| Ciprofloxacin | 93 | 3 | 1 | 1 |
| Tobramycin | 93 | 6 | 1 | 1 |

Discharge



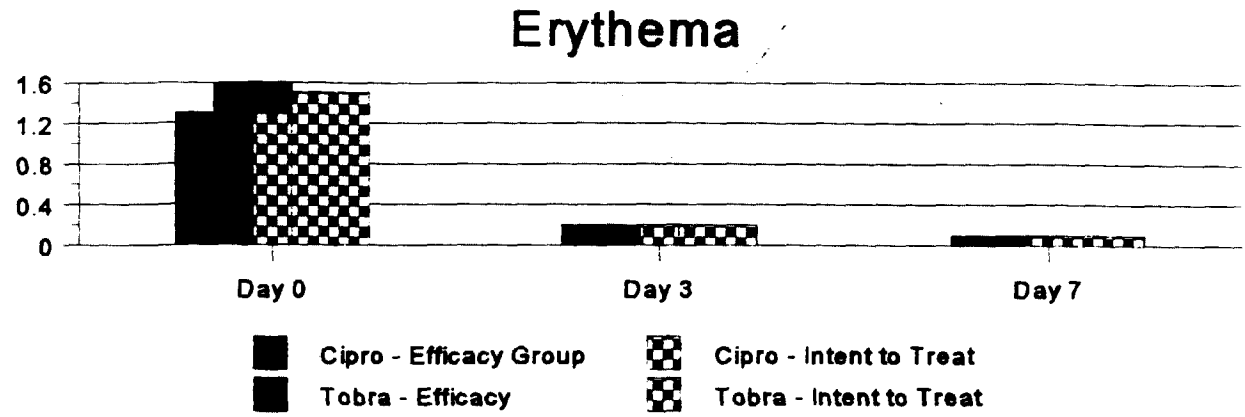

| | | | |
|---|---|---|---|
| Cipro - Efficacy Group | 1.8 | 0.3 | 0 |
| Tobra - Efficacy | 1.8 | 0.2 | 0 |
| Cipro - Intent to Treat | 1.7 | 0.2 | 0 |
| Tobra - Intent to Treat | 1.8 | 0.2 | 0 |

Bulbar Conjunctiva



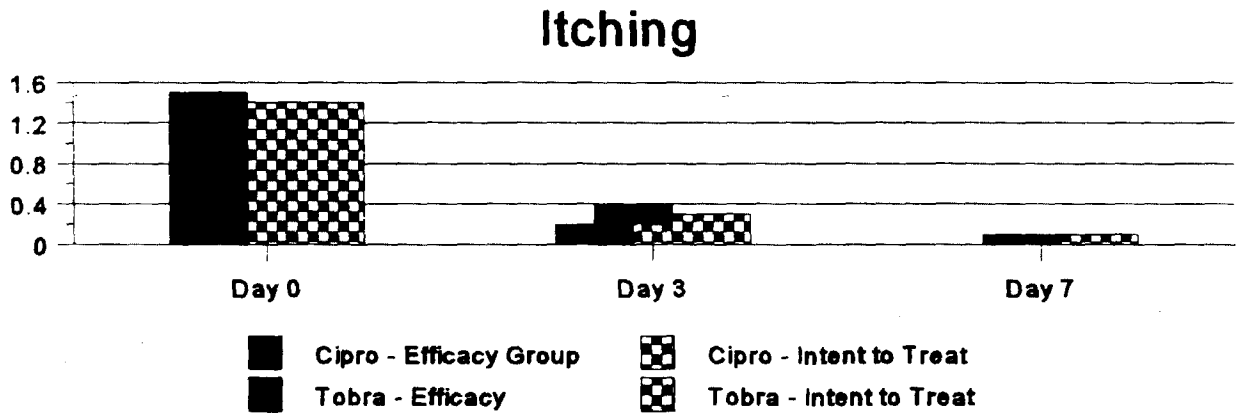

| | | | |
|---|---|---|---|
| Cipro - Efficacy Group | 1.5 | 0.2 | 0.1 |
| Tobra - Efficacy | 1.7 | 0.4 | 0.1 |
| Cipro - Intent to Treat | 1.5 | 0.3 | 0.1 |
| Tobra - Intent to Treat | 1.7 | 0.3 | 0.1 |

Erythema




| | | | |
|---|---|---|---|
| Cipro - Efficacy Group | 1.3 | 0.2 | 0.1 |
| Tobra - Efficacy | 1.6 | 0.2 | 0.1 |
| Cipro - Intent to Treat | 1.3 | 0.2 | 0.1 |
| Tobra - Intent to Treat | 1.5 | 0.2 | 0.1 |

Itching




| | | | |
|---|---|---|---|
| Cipro - Efficacy Group | 1.5 | 0.2 | 0 |
| Tobra - Efficacy | 1.4 | 0.4 | 0.1 |
| Cipro - Intent to Treat | 1.4 | 0.2 | 0 |
| Tobra - Intent to Treat | 1.4 | 0.3 | 0.1 |

**Microbiological Evaluations:**

| | Ciprofloxacin Ophthalmic Ointment | | | | | TOBREX Ointment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (n) | E | R | NC | P | (n) | E | R | NC | P |
| Gram-Positive: | | | | | | | | | | |
| *Streptococcus pneumoniae* | (23) | 19 | | 4 | | (31) | 27 | | 2 | 2 |
| *Streptococcus pyogenes* | (2) | 2 | | | | (0) | | | | |
| *Streptococcus* sp. | (2) | 2 | | | | (2) | 2 | | | |
| *Staphylococcus aureus* | (6) | 6 | | | | (5) | 5 | | | |
| *Staphylococcus epidermidis* | (1) | 1 | | | | (0) | | | | |
| *Staphylococcus*, coag. negative | (2) | 1 | | 1 | | (1) | | 1 | | |
| Gram-Negative: | | | | | | | | | | |
| *Haemophilus influenzae* | (34) | 31 | | 2 | 1 | (35) | 28 | | 7 | |
| *Moraxella catarrhalis* | (1) | 1 | | | | (2) | 2 | | | |
| Grand Total:* | (71) | 63 | 0 | 7 | 1 | (76) | 64 | 1 | 9 | 2 |
| % | (100) | (88.7) | | (9.9) | (1.4) | (99.9) | (84.2) | (1.3) | (11.8) | (2.6) |

*P=0.43; Cochran-Mantel-Haenszel Rank Score Test

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

Percents do not add to 100% due to rounding

APPEARS THIS WAY
ON ORIGINAL

Frequency and Incidence of Adverse Events

| Coded Adverse Events | Ciprofloxacin Ophthalmic Ointment 0.3% N=101[c-f] | TOBREX Ophthalmic Ointment 0.3% N=102[g,h] |
|---|---|---|
| **Ocular** | | |
| Discomfort | 1 | 1 |
| Pruritus | 1 | 0 |
| Decreased Visual Acuity | 1 | 0 |
| Blurred Vision | 0 | 1 |
| Subconjunctival Hemorrhage | 0 | 1 |
| Edema | 0 | 1 |
| Hyperemia | 0 | 1 |
| Conjunctivitis | 0 | 1 |
| **Nonocular** | | |
| Body As A Whole<br>Infection | 3 | 3 |
| Fever | 1 | 2 |
| Headache | 0 | 1 |
| Accidental Injury | 0 | 1 |
| Abdominal Pain | 0 | 1 |
| Digestive<br>Diarrhea | 0 | 1 |
| Nausea | 0 | 1 |
| Vomiting | 0 | 1 |
| Hemic and Lymphatic<br>Lymphadenopathy | 0 | 1 |
| Respiratory<br>Increased Cough | 2 | 3 |
| Pharyngitis | 2 | 3 |
| Asthma | 1 | 0 |
| Lung Disorder | 1 | 0 |
| Sinusitis | 1 | 0 |

| Coded Adverse Events | Ciprofloxacin Ophthalmic Ointment 0.3% N=101[c-f] | TOBREX Ophthalmic Ointment 0.3% N=102[g,h] |
|---|---|---|
| Bronchitis | 0 | 1 |
| Pneumonia | 0 | 1 |
| Rhinitis | 0 | 1 |
| Skin and Appendages<br>Dermatitis | 1 | 0 |
| Special Senses<br>Otitis Media | 6 | 7 |

[c] Patient Numbers 703 and 704 are the same patient OD and OS. This patient received Ciprofloxacin in one eye and TOBREX in the contralateral eye.

[d] Patient Numbers 705 and 706 are the same patient OD and OS. This patient received Ciprofloxacin in one eye and TOBREX in the contralateral eye.

[e] Patient Numbers 707, 713 and 726 are the same patient OD. This patient was enrolled three times and received Ciprofloxacin at the first enrollment and TOBREX at the second and third enrollment.

[f] Patient Numbers 721 and 724 are the same patient OD and OS. This patient received Ciprofloxacin in one eye and TOBREX in the contralateral eye.

[g] Patient Numbers 701 and 702 are the same patient OD and OS. This patient received TOBREX in one eye and Ciprofloxacin in the contralateral eye.

[h] Patient Numbers 732 and 733 are the same patient OU. This patient received TOBREX at the first enrollment and Ciprofloxacin at the second enrollment.

**Reviewer's Comments:** *The inclusion of the same patient in multiple arms of the study is a major deficiency in the study because of the possibility of cross contamination.*

**Study #6 Summary:**

1. This study has major problems including:

   A. There are discrepancies between the study report and the protocol including:
      1. The dates of the study visits, Day 3±1 vs Day 3±2.
      2. The dosing information, 1" vs ½."
      3. The drug formulation (solution formulation presented instead of an ointment).

   B. Multiple patients were enrolled more than once. This is not acceptable.

   C. There were several protocol violations including the age inclusion criteria. Patients were entered under the age of 1 and over the age of 12.

   D. The reasons why patients 2419, 2427 and 2511 did not complete the study should have been provided.

   E. There are differences in the evaluations between ophthalmologists and non-ophthalmologists.

2. No significant differences were observed between treatments, but this may be due to the poor quality of the study.

Study #7 Protocol C-91-28

Title: Ciprofloxacin Ophthalmic Ointment 0.1% is clinically and statistically equivalent to ACHROMYCIN Ophthalmic Ointment 1.0% for the treatment *Chlamydia trachomatis*.

Study Design

The objective of this study was to evaluate the efficacy and safety of Ciprofloxacin ointment versus ACHROMYCIN ointment for the treatment of conjunctivitis caused by *Chlamydia trachomatis*. Ciprofloxacin ointment and ACHROMYCIN ointment were each used TID in combination with oral tetracycline (250 mg capsules, QID) and were compared for the treatment of early chronic chlamydial conjunctivitis. For this prospective, randomized, double-masked, parallel group study, 3 investigators enrolled a total of 82 patients. Forty-three (43) patients were randomized to the Ciprofloxacin ointment treatment group and 39 patients to the ACHROMYCIN ointment treatment group. All 82 patients were evaluable for safety. One patient was enrolled twice (ACHROMYCIN ointment group both times) giving 83 patient numbers. A total of 46 patients were included in the efficacy analysis, the remaining patients being excluded for various reasons such as negative culture and loss to follow-up.

Investigators:

| | |
|---|---|
| 1108 | S. S. Badrinath, M.D.<br>Vision Research Foundation<br>18 College Road<br>Madras 600 006 INDIA |
| 362 | Delmar Caldwell, M.D.<br>Tulane University Medical Center<br>Department of Ophthalmology<br>1430 Tulane Avenue<br>New Orleans, Louisiana 70112 |
| 498 | James McCulley, M.D.<br>Univ. of Texas Southwestern Medical Center<br>Department of Ophthalmology<br>5323 Harry Hines Boulevard<br>Dallas, Texas 75235 |

APPEARS THIS WAY
ON ORIGINAL

## Mean Physician's Follow-Up Impression (0-3)

| Treatment | | Day 3 | Day 7 | Day 14 | Day 21 |
|---|---|---|---|---|---|
| **Ciprofloxacin** | MEAN | 1.38 | 1.19 | 1.05 | 0.77 |
| | STD | 0.50 | 0.40 | 0.38 | 0.69 |
| | N | 21 | 21 | 22 | 22 |
| **Achromycin** | MEAN | 1.35 | 1.33 | 1.17 | 0.88 |
| | STD | 0.49 | 0.48 | 0.38 | 0.54 |
| | N | 23 | 24 | 24 | 24 |
| Difference Between Treatments | | 0.03 | -0.14 | -0.12 | -0.11 |
| p-value | | 0.811 | 0.297 | 0.404 | 0.481 |
| Upper 95% CL | | 0.327 | 0.136 | 0.165 | 0.184 |

## Physician's Follow-Up Impression Cures

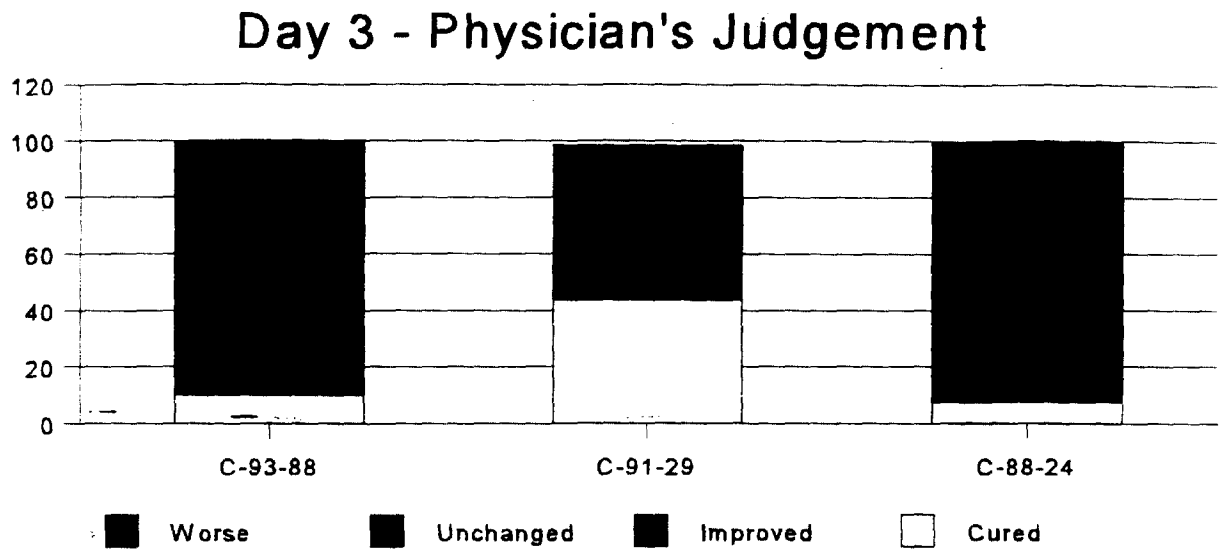
| | Ciprofloxacin | | | ACHROMYCIN | | | 95% CI for |
|---|---|---|---|---|---|---|---|
| **Visit** | **N** | **Cures** | **% Cures** | **N** | **Cures** | **% Cures** | **Diff in % Cures*** |
| **Day 3** | 21 | 0 | 0.0 | 23 | 0 | 0.0 | (0.0, 0.0) |
| **Day 7** | 21 | 0 | 0.0 | 24 | 0 | 0.0 | (0.0, 0.0) |
| **Day 14** | 22 | 1 | 4.5 | 24 | 0 | 0.0 | (-4.2, 13.2) |
| **Day 21** | 22 | 7 | 31.8 | 24 | 5 | 20.8 | (-14.4, 36.3) |

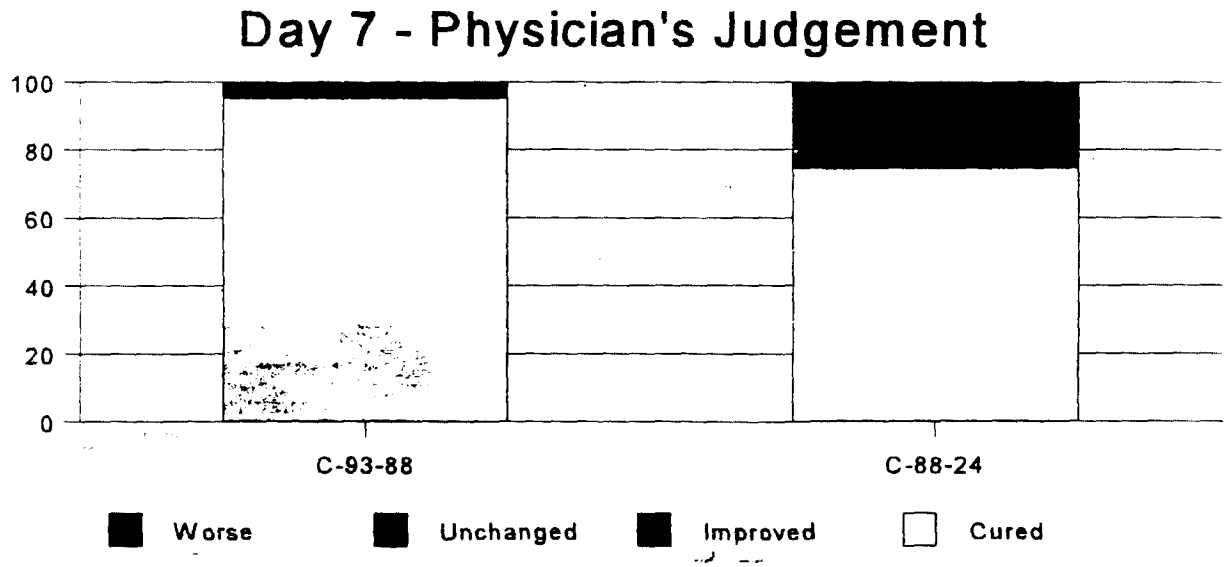
## Microbiological Treatment Efficacy (Day 21)

| | | Culture Neg | | | | IF Neg | | | | Both Culture & IF | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | NO | | YES | | NO | | YES | | Not Cured | | Cured | |
| **Treatment** | TOTAL | N | % | N | % | N | % | N | % | N | % | N | % |
| **CIPRO** | 22 | 10 | 45.45 | 12 | 54.55 | 7 | 31.82 | 15 | 68.18 | 11 | 50.00 | 11 | 50.00 |
| **ACHRO** | 24 | 6 | 25.00 | 18 | 75.00 | 5 | 20.83 | 19 | 79.17 | 9 | 37.50 | 15 | 62.50 |
| **p-values*** | | | | 0.217 | | | | 0.508 | | | | 0.552 | |
| **95% CI** | | | | -.48, .07 | | | | -.36, .14 | | | | -.41, .16 | |

**Reviewer's Comments:** *The study design does not permit an assessment of efficacy because both groups received oral tetracycline and there was a high dropout rate.*

**Summary of Efficacy**



Microbiological Eradication

| | C-93-88 | | C-91-29 | | C-88-24 | | Sum | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| *Haemophilus influenzae* | 16 | 100 | 34 | 91 | 12 | 100 | 62 | 95 |
| *Streptococcus pneumoniae* | 27 | 59 | 23 | 83 | 13 | 92 | 53 | 75 |
| *Staphylococcus aureus* | 14 | 86 | 6 | 100 | 32 | 91 | 52 | 90 |
| *Staphylococcus epidermidis* | 11 | 55 | 1 | 100 | 31 | 77 | 43 | 72 |
| Corynebacterium spp. | 6 | 100 | | | 3 | 67 | 9 | 89 |
| Acinetobacter spp. | 1 | 100 | | | 7 | 86 | 8 | 88 |
| Staphylococcus, coag_neg. | 1 | 100 | 2 | 50 | 5 | 80 | 8 | 75 |
| Streptococcus app. | 6 | 100 | | | | | 6 | 100 |
| *Streptococcus viridans* | | | | | 6 | 100 | 6 | 100 |
| Enterobacteriaceae spp. | 2 | 50 | | | 1 | 100 | 3 | 67 |
| *Moraxella catarrhalis* | 1 | 100 | 1 | 100 | 1 | 100 | 3 | 100 |
| *Streptococcus pyogenes* | 0 | | 2 | 100 | 1 | 100 | 3 | 100 |
| Klebsiella spp. | | | | | 2 | 100 | 2 | 100 |
| Micrococcus spp. | 1 | 100 | | | 1 | 100 | 2 | 100 |
| Streptococcus spp. | | | 2 | 100 | | | 2 | 100 |
| Bacillus spp. | | | | | 1 | 100 | 1 | 100 |
| Enterococcus sp. | 1 | 100 | | | | | 1 | 100 |
| Haemophilus spp. | | | | | 1 | 100 | 1 | 100 |
| Neisseria spp. | 1 | 100 | | | | | 1 | 100 |
| Proteus/Morganella spp. | | | | | 1 | 100 | 1 | 100 |
| Pseudomonas spp. | 1 | 100 | | | | | 1 | 100 |

Frequency and Incidence of Adverse Events - Number of events
Conjunctivitis Studies
(C-88-24, C-88-94, C-91-29, C-93-88)

| | Ciprofloxacin N=554 | Tobrex N=355 | Vehicle N=212 |
|---|---|---|---|
| Keratopathy* | 7 | 0 | 7 |
| Otitis Media* | 7 | 7 | 0 |
| Discomfort* | 6 | 3 | 1 |
| Pruritus* | 5 | 1 | 1 |
| Decreased Visual Acuity | 4 | 1 | 0 |
| Hyperemia* | 4 | 1 | 2 |
| Fever | 3 | 2 | 2 |
| Infection (Body as Whole)* | 3 | 5 | 0 |
| Pharyngitis | 3 | 3 | 1 |
| Chalazion/Hordeolum | 2 | 2 | 1 |
| Increased Cough | 2 | 3 | 1 |
| Pain | 2 | 1 | 0 |
| Photophobia* | 2 | 0 | 2 |
| Sinusitis* | 2 | 0 | 0 |
| Subconjunctival hemorrhage | 2 | 2 | 0 |
| Tearing | 2 | 0 | 0 |
| Allergy | 1 | 0 | 0 |
| Asthma | 1 | 0 | 0 |
| Blurred Vision | 1 | 3 | 5 |
| Bronchitis | 1 | 1 | 0 |
| Conjunctivitis | 1 | 2 | 0 |
| Corneal Staining* | 1 | 0 | 0 |
| Dacryocystitis* | 1 | 0 | 0 |
| Dehydration | 1 | 0 | 0 |
| Dermatitis | 1 | 1 | 0 |
| Diarrhea | 1 | 2 | 1 |
| Dry Eye | 1 | 0 | 1 |
| Dysmenorrhea | 1 | 0 | 0 |
| Ear Pain | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Face Edema | 1 | 0 | 0 |
| Flu Syndrome | 1 | 0 | 0 |
| Foreign Body Sensation | 1 | 0 | 0 |
| Keratitis | 1 | 1 | 0 |
| Keratoconjunctivitis | 1 | 1 | 0 |
| Lid Erythema | 1 | 0 | 1 |
| Lung Disorder | 1 | 0 | 0 |
| Lymphadenopathy | 1 | 1 | 3 |
| Meibomitis | 1 | 0 | 0 |
| Vomiting | 1 | 2 | 0 |
| Abdominal Pain | 0 | 1 | 0 |
| Accidental Injury | 0 | 1 | 1 |
| Anxiety | 0 | 0 | 1 |
| Cellulitis | 0 | 1 | 0 |
| Corneal Abrasion | 0 | 1 | 0 |
| Discharge NOS | 0 | 1 | 1 |
| Dizziness | 0 | 1 | 0 |
| Edema | 0 | 1 | 0 |
| Eye Disorder | 0 | 0 | 1 |
| Headache | 0 | 2 | 0 |
| Infiltrate | 0 | 0 | 1 |
| Iritis | 0 | 0 | 1 |
| Joint Disorder | 0 | 0 | 1 |
| Lid Disorder | 0 | 1 | 0 |
| Lid Ulcer | 0 | 0 | 1 |
| Nausea | 0 | 2 | 1 |
| Pneumonia | 0 | 1 | 0 |
| Rhinitis | 0 | 1 | 0 |
| Stromal Infiltrate | 0 | 1 | 0 |
| Taste Perversion | 0 | 1 | 0 |
| Urticaria | 0 | 0 | 1 |

* Associated with a discontinuation.

# THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

8 pages

**Conclusions/Recommendations:**

As submitted, study #6 is not considered sufficiently adequate to support the safety and efficacy of ciprofloxacin ointment, however, based on the other submitted studies, NDA 20-369 is recommended for approval for the treatment of bacterial conjunctivitis provided the following issues are satisfactorily resolved:

1. The proposed labeling should be revised as identified in this review.

2. The applicant should address the deficiencies noted in the submitted study report for protocol C-91-29. These include:
   A. Discrepancies between the study report and the protocol including:
      1. The dates of the study visits, Day 3±1 vs Day 3±2.
      2. The dosing information, 1" vs ½."
      3. The drug formulation (solution formulation presented instead of an ointment).

   B. Multiple patients being permitted to enrolled more than once.

   C. Several protocol violations occurred including the age inclusion criteria. Patients were entered under the age of 1 and over the age of 12.

   D. An explanation was not provided for the failure of patients 2419, 2427 and 2511 to complete the study.

   E. The differences in the evaluations between ophthalmologists and non-ophthalmologists were not specifically identified.

Wiley A. Chambers, M.D.

cc: Orig NDA 20-369
HFD-550
HFD-340/Carreras
HFD-550/PM/Gorski
HFD-830/CHEM/Uppoor
HFD-550/PHARM/Weir
HFD-805/MICRO/Uratani
HFD-590/MICRO/Dionne
HFD-725/STAT/Lu
HFD-550/MO/Chambers

# Medical Officer's Review of NDA 20-369
## Amendment

| | | | |
|---|---|---|---|
| **NDA 20-369** | | **Submission date:** | 1/30/98 |
| **Review #2** | | **Received date:** | 2/ 3/98 |
| Amendment | | **Review date:** | 2/17/98 |

**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

Submitted: Response to Approvable Letter dated 12/23/97.

Related Submissions:

NDA 19-992 (Ciloxan Solution)

The following items were identified in the approvable letter, together with the applicant's responses:

**Applicant's Response:** Alcon agrees that the drug substance raw material will not be at an alternate site without appropriate approval.

**Reviewer's Comments:** *Acceptable.*

**Applicant's Response:** Alcon agrees to eliminate the overage.

**Reviewer's Comments:** *Acceptable.*

**Applicant's Response:** "It is noted that the Draft ICH Guidelines provide, in general, for label storage conditions of up to 30°C when stability is tested at 25°C. Alcon recognizes that this is not applicable to ointments because of their unique physical properties. Therefore we agree to revise the label accordingly.

**Reviewer's Comments:** *Acceptable. The reported "Draft ICH Guideline for labeling at up to 30° when stored at 25°" is not appropriate for any ophthalmic drug product.*

**Applicant's Response:** A full response to each FDA-483 observation has been made and submitted to the San Juan District office on 1/20/98.

**Reviewer's Comments:** *Awaiting comments from District office.*

**Applicant's Response:** "Following please find draft labeling ....:"

# THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5 pages

**Applicant's Response:**

... the correct window for this optional visit is 3±2 days as stated in the protocol, ... a half-inch ribbon was used as stated in the protocol, ... The correct lot numbers and formulation information are provided and replace the information provided on page 8-0731 of the CMR.

Alcon has conducted a comprehensive audit of studies C-91-29, C-88-23, C-93-88, C88-24, C-88-94, C-88-24, C-88-43, C-90-122, C-91-22, C-91-28, C-90-85, and C-90-52. The audit results indicate that minor errors or oversights were made. None of these errors, however, significantly affect the overall outcome and conclusions reached in each study regarding the safety and/or efficacy of CILOXAN Ophthalmic Ointment.

Alcon continues its commitment to report clinical studies at the highest level to ensure the accuracy of its CMRs. Since the time these studies were conducted and reports were issued, significant improvements have been made in our quality assurance program. A training program is in place that addresses the type of observations noted in the study audits."

**Conclusions/Recommendations:**

Pending results from the re-inspection of the manufacturing site, NDA 20-369 is recommended for approval for the treatment of bacterial conjunctivitis.

Wiley A. Chambers, M.D.

cc: Orig NDA 20-369
HFD-550
HFD-340/Carreras
HFD-550/PM/Gorski
HFD-830/CHEM/Uppoor
HFD-550/PHARM/Weir
HFD-805/MICRO/Uratani
HFD-590/MICRO/Dionne
HFD-725/STAT/Lu
HFD-550/MO/Chambers