CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-369

STATISTICAL REVIEW(S)

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Statistical Review and Evaluation

NDA #: 20-369/1C

Applicant: Alcon Laboratories Inc

Name of Drug: Ciprofloxacin HCL (CILOXAN) Ointment

Documents Volumes 1 through 8 dated 24th May, 1993

Indication: Bacterial Conjunctivitis (Page 1) and Bacterial Corneal Ulcer (Page 5)

Clinical Input: Jose Careras, M.D.

1. Introduction: The sponsor has submitted **two** multicenter clinical trials to demonstrate the safety and efficacy of Ciprofloxacin HCl Ophthalmic Ointment (0.3% as base) in the treatment of **bacterial conjunctivitis.** One multicenter study (C-88-24) compared Ciprofloxacin Ointment to Tobramycin 0.3% (TOBREX), a marketed broad-spectrum antibiotic that has been proven to be effective and safe in treating ocular bacterial infections. In the second multicenter study (C-88-94), Ciprofloxacin was evaluated against Placebo.

The sponsor has also submitted **two** multicenter studies (Study 1: Investigators from the east of Mississippi river; Study 2: Investigators from the west of Mississippi river) to demonstrate that ciprofloxacin ointment 0.3% is effective in the treatment of **bacterial corneal ulcers.** Both studies were carried out under the same protocol (C-90-85), which was open-label, multicenter and historically-controlled. Each patient in Protocol No. C-90-85 dosed the coded medication for up to 14 ($\pm$2) days, or longer if prescribed by the patient's ophthalmologist. The results from the ciprofloxacin ointment studies (1 and 2) were compared to three control groups: (1) the "Solution" Group (C-88-88; NDA 19-992) involved 148 evaluable patients (i.e., had a positive bacterial culture and a Final Physician Judgment); (2) the "Historical" Control Group (C-90-52) was comprised of 103 evaluable patients treated with "standard" antibacterial therapies of the physicians' choices within one year prior to the physicians enrolling patients into the ciprofloxacin solution study C-88-88) (these data were obtained retrospectively); and (3) the "Not Enrolled" Group (C-90-94) consisting of 40 evaluable patients who were ineligible for enrollment in the ciprofloxacin group because reasons such as, (a) Ulcer involves patient's only good eye, (b) Perforation imminent, (c) Patients with known or clinically suspected fungal keratitis, and (d) Patient refusing to enter the ciprofloxacin ointment study, and were treated prospectively with standard therapy. Data from the "Solution" and the retrospective "Historical" group were collected during clinical trials with the solution dosage form and reported in NDA 19-992, which was approved.

In the bacterial corneal ulcer trials, the comparisons will be carried out within study, i.e., Study 1 data for ciprofloxacin ointment will be compared to Study 1 data for ciprofloxacin solution, Study 1 data for standard therapy and Study 1 data for historical controls. These same comparisons will be performed for Study 2.

In the following sections the order of values in the confidence intervals is $_{pt,pc}(-.LL,.UL)_{nt,nc}$, where p_t is the proportion of successes for the test drug, p_c is the proportion of successes for the active control drug, LL and UL are respectively the lower and upper limits of the confidence interval, n_t and n_c are the number of observations in the test drug arm and the active control drug arm. To demonstrate efficacy, the 95% CIs must meet the Divisional delta limits (10% for 90% success rates, 15% for 80% success rates and 20% for less than 80% success rates) for both clinical cure rates and pathogen elimination rates.

II. Review Studies:

1. Study C-88-24 (Bacterial Conjunctivitis)

a. Study design, study population and demographics:

This is a randomized, controlled, double-masked, multicenter comparison of the efficacy and safety of Ciprofloxacin Ophthalmic Ointment 0.3% and Tobrex Ophthalmic Ointment. Thirty six investigators in 27 cities participated in this multiclinic evaluation with 28 contributing patients.

A total of 500 patients were enrolled in this study. Three of these patients were not issued drug or dosed, leaving 497 patients that were included in the analysis for safety. Of the 497 patients, 178 patients were diagnosed with acute bacterial conjunctivitis (Ciprofloxacin = 87, Tobrex = 91), were culture-positive for bacteria, met all other protocol requirements and thus were included in the efficacy analysis (culture-positive group). Of the 319 non-evaluable patients, 287 were culture-negative and 38 did not complete the study for reasons such as, day 7 missing data, day 7 out of range, invalid last instillation time and non-compliance day 7. A total of 497 patients were evaluated for efficacy in the intent-to-treat group. This group was comprised of patients with clinically diagnosed acute bacterial conjunctivitis, regardless of microbiological culture results. Patients were considered to be evaluable for antibacterial efficacy if they were conjunctival culture-positive on Day 0, dosed with medication for at least six days and returned for their Day 7 ($\pm$ 2 days) follow-up exam and culture.

The efficacy of Ciprofloxacin Ophthalmic Ointment 0.3% relative to Tobramycin was determined by evaluating three parameters: the bacteriological results of the conjunctival specimens at Day 7 ($\pm$ 2 days) relative to Day 0, the physician's clinical judgement at Day 7 ($\pm$ 2 days) regarding overall resolution of disease and severity scores assigned to the five cardinal clinical signs of conjunctivitis such as, erythema, exudation, discharge, and palpebral and bulbar conjunctival inflammation.

For both culture-positive and intent-to-treat groups, the two treatment groups are not statistically significantly different relative to age ($p > 0.09$), gender ($p > 0.14$) and race ($p = > 0.60$). The distribution of unilateral versus bilateral infections between the two treatment groups was not significantly different in the culture-positive group ($p = 0.66$) or in the intent-to-treat ($p = 0.41$). The length of disease in culture-positive evaluable patients before entering the study ranged from 1-30 days in the ciprofloxacin group and 1-42 days in the tobramycin group. No statistical differences within the two treatment

groups were discernible ($p = 0.11$). There was no difference between treatment groups in the number of days that patients experienced conjunctivitis in the intent-to-treat group ($p = 0.72$). Treatment comparisons for days on treatment indicate no significant differences in either culture-positive group (p-0.40) or the intent-to-treat group ($p = 0.57$).

b. Efficacy results:

Ciprofloxacin was not statistically significantly worse than Tobrex for **microbiological efficacy** (95% C.I. for the difference (Cipro. - Tobrex) is $_{(91,87)}(-.01,.18)_{(95\%,87\%)}$). The primary variables in evaluating the clinical efficacy of Ciprofloxacin versus Tobramycin are the physician's judgment and clinical cardinal signs. The physician, on each follow-up examination day (Days 3 and 7), evaluated the patient as cured, better, unchanged or worse relative to baseline. Ciprofloxacin was statistically not worse than Tobrex for clinical efficacy on Day 7, the 95% C.I. for the difference (Cipro. - Tobrex) is $_{(87,91)}(-.005,.136)_{(99\%,92\%)}$. The 95% CI for the difference (Cipro - Tobrex) for Day 3, $_{(39,42)}(-.195,.129)_{(90\%,87\%)}$, though includes zero, does not satisfy the delta limits of the Division of Anti-Infective Drugs and Drug Products.

The cardinal signs associated with conjunctivitis are exudation, erythema, discharge and palpebral and bulbar conjunctival inflammation. Ciprofloxacin was not statistically different from tobrex in reducing the severity of each of the clinical cardinal signs of conjunctivitis in both study groups on days 3 and 7 ($p > 0.05$).

c. Safety results: (Reviewer's analysis)

There are statistically no significant differences between Ciprofloxacin and Tobrex relative to the frequency and incidence of medical events (Related[1]: Chi-square p-value, $p = 0.205$, Not related[2]: Chi-square p-value, $p = 0.372$).

d. Conclusions:

Study C-88-24 shows that Ciprofloxacin 0.3% is not statistically worse than Tobrex in the treatment of bacterial conjunctivitis, both microbiologically (95% C.I. for (Cipro - Tobrex) is $_{(91,87)}(-.01,.18)_{(95\%,87\%)}$) and clinically (95% C.I. for (Cipro-Tobrex) is $_{(87,91)}(-.005,.136)_{(99\%,92\%)}$ for Day 7). Further, Ciprofloxacin is as safe as Tobrex in the treatment of bacterial conjunctivitis.

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[1] Related = Possibly, Probably or Definitely related.

[2] Not related = Unlikely or Definitely Unrelated

2. Study C-88-94 (Bacterial Conjunctivitis)

a. Study design, study population and demographics:

This is a randomized, controlled and double-masked comparison of the efficacy and safety of Ciprofloxacin Ophthalmic Ointment 0.3% and Placebo (Vehicle). Ten investigators at seven cities participated in this multiclinic evaluation. A total of 144 patients were evaluable for safety and 71 (49%) conjunctivitis patients (29 in Ciprofloxacin groups and 49 in Placebo group) were evaluable for efficacy. The 73 (51%) patients were non-evaluable for efficacy because, most of them were culture-negative. The efficacy of Ciprofloxacin was determined in the same way as is done in Study C-88-24.

No significant treatment differences were found for any of the demographic characteristics of the culture-positive patients ($p > 0.28$). No significant treatment differences were observed for the intent-to-treat group with respect to age, sex or race ($p > 0.59$). The distribution of unilateral versus bilateral infections between the two treatment groups was not significantly different for the culture-positive ($p = 0.85$) or the intent-to-treat ($p = 0.70$) groups. The length of disease in culture-positive patients before entering the study was not significantly different between treatment groups ($p = 0.42$). No statistical difference ($p = 0.16$) was observed in the intent-to-treat group as well. The number of days that patients were treated with study medication was not significantly different between treatments (culture positive, $p = 0.16$; intent-to-treat, $p = 0.56$).

b. Efficacy results:

No statistically significant treatment differences were found for the comparison of **microbiological resolution** scores in culture-positive patients (Eradicated: Cipro = 20/29 Placebo = 21/42 and Cochran Maentel Haenszel p value, $p = 0.08$). The sponsor combined the eradication and reduction counts and showed that there was statistically significant difference between the two treatment groups ($p = 0.04$). According to the reviewing medical officer, combining eradication and reduction counts, is not an acceptable practice. The physician, on each follow-up examination day (Days 1, 2, and 3), evaluated the patient as cured, better, unchanged or worse relative to baseline. When the scores for each treatment group was compared, no statistically significant treatment difference was found ($p = 0.34$) in the culture-positive group. The sponsor dropped one investigator (No. 1523) who clinically rated each of his 24 evaluable patients as cured or better. The clinical results of 33% (8/24) of these patients did not corroborate their microbiological results. Furthermore, of the 47% (17/37) patients in this study whose physician judgments disagreed with their microbiological outcomes, 47% (8/17) were contributed by this investigator. The sponsor's analysis of physician judgment ratings, excluding this investigator, showed statistically significant differences between ciprofloxacin and placebo ($p = 0.02$). Investigator (No. 1523) contributed to 33% (24/71) of the evaluable patients. The reasons cited for dropping this investigator from the analysis is not defensible.

The five cardinal signs most frequently associated with conjunctivitis are exudation, erythema, discharge and palpebral and bulbar conjunctival inflammation. The sponsor's analyses of the improvement scores of these five signs showed that ciprofloxacin was statistically significantly more effective than placebo for palpebral conjunctival inflammation on Day 2 in the culture-positive group. In the intent-to-treat group, ciprofloxacin was significantly more effective than placebo for bulbar conjunctival inflammation on Day 2 ($p = 0.046$) and palpebral conjunctival inflammation on Day 3 ($p = 0.02$). No other statistically significant treatment differences were found for any of the other cardinal signs at any follow-up visit.

c. Safety results: (Reviewer's analysis)

There are statistically no significantly differences between Ciprofloxacin and Placebo, relative to the frequency and incidence of medical events (Related[3]: Chi-square p-value, $p = 0.271$, Not related[4]: Chi-square p-value, $p = 0.912$).

d. Conclusions:

Study C-88-94 fails to support the sponsor's claim that Ciprofloxacin Ophthalmic Ointment 0.3% is effective in the treatment of bacterial conjunctivitis.

3. Study C-90-85 - Studies 1 and 2 (Corneal Ulcer)

a. Study design, study population and demographics

This prospective, open-label and multicenter (investigators from east and west of Mississippi river) study was conducted to determine the efficacy and safety of Ciprofloxacin Ointment 0.3% for treating bacterial ulcers. The cure rates obtained with the solution, with "historical" standard therapy and with standard therapy for patients "not enrolled" in the ciprofloxacin study were each used as a control. Three parameters were used to measure efficacy: physician's judgments, re-epithelialization of the corneal defect and changes in ocular signs and symptoms.

Of the 166 patients enrolled in the study, 166 were evaluable for safety and 106 (64%) were evaluable for efficacy. Of the sixty (36%) non-evaluable patients, 43 were culture negative upon enrollment and the remaining 17 were excluded for reasons such as lost-to-follow-up, concomitant therapy used, systemic antibiotic used no day 0 culture done etc.

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[3] Related = Possibly, Probably or Definitely related

[4] Not related = Unlikely, or Definitely Unrelated

b. Efficacy analyses (by the sponsor and checked by the reviewer)

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

The sponsor compared the data for 106 Ciprofloxacin Ointment patients to 86 Ciprofloxacin Solution patients. 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 ($p > 0.09$). The sponsor's analysis showed that, relative to physician's final judgement, Ciprofloxacin Ointment is significantly more effective for treatment of corneal ulcers than Ciprofloxacin solution (Cochran-Maentel-Haenszel Rank Score Test Statistic p-value: $P < 0.01$ and the 95% CI for the difference in cure rates, (Cipro Ointment - Cipro Solution) is $_{(106,86)}(.043,.289)_{(89\%,72\%)}$). The sponsor performed an additional analysis 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 Day 0 ulcer size.

Ciprofloxacin Ointment (C-90-85) vs. Ciprofloxacin Solution (C-88-88): Study 2

The sponsor compared the data for 39 Ciprofloxacin Ointment patients to 62 Ciprofloxacin Solution patients. 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 (24.1% against 5.1%; $p = 0.049$), but no significant differences were observed at Day 0 for ulcer duration or ulcer depth ($p > 0.14$).

The sponsor's analysis showed that Ciprofloxacin Ointment is not statistically different from Ciprofloxacin Solution relative to physician's final judgement (Cochran-Maentel-Haenszel Rank Score Test Statistic p-value, $p = 0.76$ and the 95% CI for the difference in cure rates, (Cipro Ointment - Cipro Solution) is $_{(39,62)}(-.192,.145)_{(85\%,82\%)}$). The 95% CI, though it includes zero, does not satisfy the delta criterion of the Division of Anti-Infective Drugs and Drug Products, because it fails to meet a therapeutic equivalency criterion of -.15,. Since the Ciprofloxacin solution study had significantly more patients with ulcer diameters larger than 4 mm, an additional analysis, to adjust for differences in ulcer diameter, was performed. No significant differences were found after adjusting for ulcer size ($p = 0.92$).

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

Ciprofloxacin Ointment (C-90-85) vs. Standard Therapy (C-90-94): Study 1

The sponsor compared data for 106 Ciprofloxacin Ointment patients to 27 Standard Therapy patients from Protocol C-90-94. No significant differences were found for age, sex or race ($p > 0.23$) or Day 0 ulcer diameter, depth or duration ($p > 0.17$).

The sponsor's analysis showed that physicians judged Ciprofloxacin Ointment to be significantly more effective for the treatment of corneal ulcers than standard therapy (Cochran-Maentel-Haenszel Rank Score Test Statistics p-value, $p < .01$ and the 95% CI for the difference in cure rates, (Cipro Ointment- Std. Therapy) is $_{(106,27)}(.009,.431)_{(89\%,67\%)}$).

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 ($P<0.001$) after adjusting for ulcer size.

Patients not enrolled in C-90-85 were on Standard Therapy significantly longer than Ciprofloxacin Ointment patients ($p=0.03$). Significantly more non-enrolled patients on standard therapy were treatment failures ($p<0.001$).

Ciprofloxacin Ointment (C-90-85) vs. Standard Therapy (C-90-94): Study 2

The sponsor's analyses compared the data for 39 Ciprofloxacin Ointment patients to 13 non-enrolled standard therapy patients from Protocol C-90-94. All statistical results should be interpreted with some degree of caution due to the small sample sizes and resultant lack of power to rule out relatively large differences in cure rates. 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 ($p>0.14$).

No significant treatment differences were found for physician's judgement due to the small number of patients in the Standard Therapy group (Cochran-Maentel Haenszel Rank Score Test Statistic, p-value, $p=0.55$ and the 95% CI on the difference in cure rates (Cipro. Ointment - Std. Therapy) is $_{(39,13)}(-.230,.384)_{(85\%,77\%)}$). This confidence interval, though includes zero, does not satisfy the delta criterion of the Division of Anti-Infective Drugs Products because of the small number of patients in Standard Therapy.

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 ($p=0.29$). 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.

Ciprofloxacin Ointment (C-90-85) vs. Historical Patients (C-90-52): Study 1

The sponsor's analyses compared data for 106 Ciprofloxacin Ointment patients to 71 historical database patients who were on standard therapy (C-90-52). The historical database was derived from 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.

The sponsor's analyses showed that Ciprofloxacin Ointment was significantly more effective for the treatment of corneal ulcers than historical standard therapy (Cochran-Maentel-Haenszel Rank Score Test Statistic p-value, $p<0.001$ and the 95% CI on the difference in cure rates (Cipro Ointment - Hist. Std. Therapy) is $_{(106,71)}(.168,.451)_{(89\%,58\%)}$.

Since the Historical study had significantly more patients with ulcer diameters larger than 4 mm, an additional 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 ($p<0.001$).

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 ($p<0.001$).

Ciprofloxacin Ointment (C-90-85) vs. Historical Patients (C-90-52): Study 2

The sponsor's analyses compared the data for 39 Ciprofloxacin Ointment patients to 32 historical database patients who were on standard therapy (C-90-52). The historical database was derived from 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.

No significant treatment differences were detected for physicians judgement (Cochran-Maentel-Haenszel Rank Score Test Statistic p-value, $p=0.31$ and the 95% CI on the difference in cure rates, (Cipro. Ointment - Hist. Std. Therapy) is $_{(39,32)}(-.120,.313)_{(85\%,75\%)}$). Since the Historical study had significantly more patients with ulcer diameters larger than 4 mm (29.0% (Hist.) vs. 5.1 (Cipro)), a second analysis, to adjust for differences in ulcer diameter, also indicated no significant treatment differences ($p=0.23$). 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 ($p<0.001$).

Analyses of Studies 1 and 2 combined (by the reviewer)

Comparison of the Physician's Final Judgement in Studies 1 and 2 combined, revealed the following:

(1) Ciprofloxacin Ointment is more effective for treatment of corneal ulcers than Ciprofloxacin Solution (95% CI for the difference (Cipro. Ointment - Cipro. Solution) is $_{(145,148)}(.019,.206)_{(88\%,76\%)}$ and the Cochran-Maentel-Haenszel Rank Score Statistic p-value, $p=0.019$).

(2) Ciprofloxacin Ointment is more effective for treatment of corneal ulcers than Standard therapy treatment (95% CI for the difference (Cipro. Ointment - Std. Therapy) is $_{(145,40)}(.008,.347)_{(88\%,70\%)}$ and the Cochran -Maentel-Haenszel Rank Score Statistic p-value, $p=0.011$).

(3) Ciprofloxacin Ointment is more effective for treatment of corneal ulcers than Historical Standard therapy treatment (95% CI for the difference (Cipro Ointment - Hist. Std. Therapy) is $_{(145,103)}(.129,.361)_{(88\%,63\%)}$ and the Cochran-Maentel-Haenszel Rank Score Statistic p-value, $p=0.000$).

c: Secondary Analyses (by the reviewer):

The reviewer performed a secondary analysis on the major clinical signs such as Epithelial Disease, Focal Stromal Infiltrates, Cells, Flare, Discharge and Erythema at Off Therapy, associated with Corneal Ulcers and found the following:

(1) In Studies 1 and 2, Ciprofloxacin Ointment is not statistically different from Ciprofloxacin Solution ($p>0.05$) at Off-Therapy, relative to all the major clinical signs.

(2) In Study 1, Ciprofloxacin Ointment is not statistically better than Standard Therapy ($p>0.05$), relative to **Epithelial Disease, Cells, Flare and Erythema** at Off-Therapy. However, relative to **Focal Stromal Infiltrates and Discharge**, Ciprofloxacin Ointment is statistically better than Standard Therapy ($p<0.05$) at Off-Therapy. But this should be interpreted with caution, because of small number of patients in the Standard Therapy regimen.

(3) In Study 2, the number of patients in the Standard Therapy regimen is too small to do any appropriate statistical analysis.

d. Safety results:

Ciprofloxacin Ointment 0.3% was evaluated for safety in 166 patients in Study 1 and in 87 patients in Study 2, 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.

e. Conclusions:

Study 1 provides statistical support to the sponsor's claim that **Ciprofloxacin Ointment 0.3%** is better than Ciprofloxacin Solution (95% CI on (Cipro. Oint - Cipro Solution) is $_{(106,86)}(.043,.289)_{(89\%,72\%)}$, Standard Therapy (95% CI on (Cipro. Oint n- Std.Therapy) is $_{(106,27)}(.009,.431)_{(89\%,67\%)}$) and Historical Standard Therapy (95% CI on the difference (Cipro. Oint - Hist. Std Therapy is $_{(106,71)}(.17,.45)_{(89\%,58\%)}$).

Although Study 2, supports the sponsor's claim that Ciprofloxacin Ointment 0.3% is not statistically **worse** than Ciprofloxacin Solution (95% CI on the difference (Cipro Oint - Cipro Soln) is $_{(39,62)}(-.192,.145)_{(85\%,82\%)}$) and Standard Therapy (95% CI on the difference (Cipro Oint - Std. **Therapy**) is $_{(39,13)}(-.23,.38)_{(85\%,72\%)}$), it does not have enough power to rule out the possibility that Ciprofloxacin Ointment 0.3% is atleast 20% less effective than Ciprofloxacin Solution and Standard Therapy. However this study provides statistical support to the sponsor's claim that Ciprofloxacin Ointment is better than Historical Standard Therapy (95% CI on the difference (Cipro Oint - Hist. Std Therapy) is $_{(39,12)}(-.120,.313)_{(85\%,75)}$).

Study 1 or Studies 1 and 2 combined, provides statistical support to the sponsor's claim that Ciprofloxacin Ointment 0.3% is better than Ciprofloxacin Solution,Standard Therapy and Historical Standard Treatment, the Cochran-Maentel-Haenszel Rank Score Statistic p-value are, $p=0.019$, $p=0.011$ and $p=0.000$, respectively.

Further, these studies demonstrate that Ciprofloxacin Ointment 0.3% lacked ophthalmic and systemic toxicity and was well tolerated by patients with bacterial corneal ulcers.

III. Overall conclusions (which may be conveyed to the sponsor)

Study C-88-24 provides statistical evidence to support the sponsor's claim that **Ciprofloxacin Ointment 0.3%** is not worse than **Tobrex** (95% CI for (Cipro Oint - Tobrex) is $_{(87,91)}(-.005,.136)_{(99\%,92\%)}$ for Day 7). in the treatment of **Bacterial Conjunctivitis.**

Study C-88-94 fails to provide statistical evidence to support the sponsor's claim that **Ciprofloxacin Ointment 0.3%** is better than **Vehicle** (Cochran-Maentel-Haenszel Test Statistic p-value, $p=0.08$ for the comparison of Microbiological Resolution scores in the culture-positive patients) in the treatment of **Bacterial Conjunctivitis.**

Study 1 or Studies 1 and 2 combined (C-90-85), provides statistical evidence to support the sponsor's claim that **Ciprofloxacin Ointment 0.3%** is better than **Ciprofloxacin Solution (p = 0.019), Standard Therapy (p = 0.011) and Historical Standard Treatment (p = 0.000)** in the treatment of **Bacterial Corneal Ulcers.**

Thus, only the active-controlled study (C-88-24) provides statistical evidence to support the sponsor's claim that **Ciprofloxacin Ointment 0.3%** is not worse than **Tobrex** in the treatment of **Bacterial Conjunctivitis.** The vehicle-controlled study **fails** to provide statistical evidence to support the sponsor's therapeutic equivalency claim.

Study 1 or Studies 1 and 2 combined (C-90-85), provides statistical evidence to support the sponsor's claim that **Ciprofloxacin Ointment 0.3%** is better than **Ciprofloxacin Solution, Standard Therapy and Historical Standard Therapy** in the treatment of patients with **Bacterial Corneal Ulcers.**

Based on these analyses, the sponsor needs an additional independent, adequate, well-controlled study to support their **Bacterial Conjunctivitis** claim as well as another independent and well-controlled clinical study to support their **Bacterial Corneal Ulcer** claim.

R.Srinivasan Ph.D
Mathematical Statistician

2/14/94

Concur: Dr. Harkins

Dr. Dubey 2-15-94

cc:
Orig NDA 20-369

HFD-540
HFD-540/Dr. Gavrilovich
HFD-540/Dr. Chambers
HFD-540/Dr. Carreras
HFD-540/Ms. Joyce
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-713/Dr. Srinivasan
HFD-344/Dr. Lisook

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Statistical Review and Evaluation

OCT 21 1997

NDA 20-369
Name of Drug: CILOXAN Ophthalmic 0.3% Ointment (cirofloxacin hydrochloride ophthalmic ointment)
Applicant: Alcon Laboratories
Indication: Treatment of Bacterial Conjunctivitis
Documents Reviewed: Statistical Section of NDA 20-369 (Vol. 6-Vol. 16) Dated 6/24/97 by CDER
Reviewer: Laura Lu, Ph.D.
Date of Review: 10/20/97

I. Background

The original application of NDA 20-369 was submitted to the FDA on May 24, 1993. The FDA advised that the application was not approvable since the studies submitted were not sufficient to support the indication for 'treatment of bacterial conjunctivitis and bacterial corneal ulcers'. In the current submission, the proposed package insert has been revised to reflect an 'Indications and Usage' section that only includes conjunctivitis. As requested by the FDA, one new study (Study C-93-88) comparing CILOXAN ointment to placebo and a second new study (Study C-91-29) comparing CILOXAN ointment to an active control TOBREX in pediatric patients (age<=12) were conducted. These two new studies and one original study C-88-24, which compares CILOXAN ointment to TOBREX , are the three pivotal studies of NDA 20-369.

II. Study C-93-88

1. Protocol

This is a randomized, triple masked, placebo controlled, and parallel group study conducted in multiple centers. The objective of this study is to determine the clinical and microbiological efficacy and safety of Ciprofloxacin Ophthalmic Ointment for treating acute bacterial conjunctivitis. A total of 130 patients (age >= 2) will be included in the study with 65 patients included in each treatment group. Patients will 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 am, 3pm, and 9pm) on days 1 and 2; then twice a day while awake (approximately 9 am and 9 pm) on Day 3.

There are two primary statistical endpoints: Physician Impression at Day 4 over four categories (Cured, Better, Unchanged, and Worse) and comparison of the Day 1 and Day 4 microbiological cultures evaluated over four categories (Eradication, Reduction, Persistence, and Proliferation). Secondary endpoints are the four cardinal clinical signs for conjunctivitis (Exudation/Discharge, Bulbar Conjunctiva, Erythema/Swelling and Palpebral Conjunctiva). A nonparametric test (rank sum or equivalent) will be used with 5% two sided significance

level. Using the results of a previous study, C-87-04/C-87-22, the power to detect a 20% difference in the percentage of patients cured is 80% with the current sample size (65 patients per treatment group). This sample size will be sufficient for both the Physician Impression and the microbiological culture data. The above calculation is based on a rank sum test adjusted for ties with 5% two sided significance level.

2. Sponsor's Results

Patients' Evaluability

A total of 277 patients with clinically diagnosed bacterial conjunctivitis were enrolled in this study by eight investigators. Of these patients, 139 were randomized into the ciprofloxacin treatment group and 138 into the placebo treatment group. All 277 enrolled patients were dosed with the study drug and were evaluable for safety as well as intent-to-treat analysis. Among the 277 patients, 140 patients were evaluable for efficacy. The reasons for unevaluability are listed as follows.

Patients Excluded from Efficacy Analyses for Microbiological Reasons			
Reason	Ciprofloxacin	Placebo	Total
Negative Culture	70	61	131
Invalid Culture	0	1	1
No Culture Results	1	0	1
Total	71	62	133

Culture-Positive Patients Excluded from Efficacy Analyses			
Reason	Ciprofloxacin	Placebo	Total
No follow-up culture	0	3	3
Culture taken on Day 5	0	1	1
Total	0	4	4

Demographics

No statistically significant differences were found in demographic and baseline characteristics between the treatment groups. The information for sex, age and race for both the intent-to-treat population and efficacy population is summarized in the table below. The P-values are based on Fisher's Exact test (for sex and age) and Cochran-Mantel-Haenszel test (for race).

Demographic Characteristics of the Efficacy Population

	Sex (p=0.13)		Age (p=0.51)		Race (p=0.13)		
	Male	Female	Mean	Std	Caucasian	Black	Other
Cipro	24	44	21.9	19.9	49	10	9
Placebo	28	44	24.3	22.6	50	5	17

Demographic Characteristics of the Intent-to-Treat Population

	Sex (p=0.96)		Age (p=0.51)		Race (p=0.13)		
	Male	Female	Mean	Std	Caucasian	Black	Other
Cipro	53	86	25.5	19.0	106	14	19
Placebo	53	85	27.7	20.8	98	8	30

Clinical Efficacy

The efficacy results reported here are for the efficacy population (patients evaluable for efficacy) only. The results of the intent-to-treat population were consistent with that of the efficacy population. Ciprofloxacin ointment was clinically and statistically significantly more effective than placebo for the Physician Impression on Days 2 and 4 in the efficacy population ($p = 0.02$, $p = 0.04$). Table 13b on Page 8-0186 of NDA 20-369 summarizes the Physician Impression in the efficacy population for both ciprofloxacin and placebo stratified by sex, race and age category at each Day. Results for the Physician Impression were clinically similar for male and female patients, Caucasian and non-Caucasian patients and patients who were 0-12 years, 13-64 years and 65 years or older. The study results for the Physician Impression of the efficacy population on Day 4 are listed as follows.

Physician Impression

		Total	Cured		Improved		Unchanged		Worse		
Day	Treatment		N	%	N	%	N	%	N	%	p*
4	Ciprofloxacin	68	32	47.1	34	50.0	1	1.5	1	1.5	0.04
	Placebo	72	23	31.9	43	59.7	3	4.2	3	4.2	

* Cochran-Mantel-Haenszel Rank Score Test

The scores for Discharge/Exudate, Erythema/Swelling, Palpebral Conjunctival Hyperemia and Bulbar Conjunctival Hyperemia were compared between the two treatment groups at each visit. For the efficacy population, the overall cardinal signs results (raw means) are as follows:

Cardinal Signs

Treatment Group	Statistics	DAY 1	2	3	4
		DISCHARGE			
Cipro	Mean (Std)	2.1 (0.60)	0.9 (0.69)*	0.4 (.57)	0.2 (0.48)*
Placebo	Mean (Std)	1.9 (0,69)	1.2 (0.71)	0.6 (0.80)	0.4 (0.62)
		BULBAR CONJUNCTIVAL HYPEREMIA			
Cipro	Mean (Std)	1.8 (0.63)	1.2 (0.59)	0.8 (0.60)	0.4 (0.62)
Placebo	Mean (Std)	1.9 (0.63)	1.3 (0.58)	1.0 (0.72)	0.6 (0.76)
		ERYTHEMA			
Cipro	Mean (Std)	1.4 (0.67)	0.8 (0.66)	0.4 (0.55)	0.1 (0.50)*
Placebo	Mean (Std)	1.3 (0.66)	1.0 (0.65)	0.6 (0.72)	0.3 (0.59)
		PALPEBRAL CONJUNCTIVAL HYPEREMIA			
Cipro	Mean (Std)	1.6 (0.65)	1.2 (0.59)	0.8 (0.70)*	0.4 (0.61)
Placebo	Mean (Std)	1.7 (0.67)	1.3 (0.66)	1.0 (0.71)	0.6 (0.74)

*: $p < 0.05$, Cochran-Mantel-Haenszel Rank Score test

Microbiological Efficacy

Overall, ciprofloxacin ointment was microbiologically superior to placebo. The following table shows Day 4 treatment efficacy data for ciprofloxacin ointment versus placebo. Table 12b on Page 8-0185 of NDA 20-369 summarizes Day 4 treatment efficacy data for ciprofloxacin ointment versus placebo stratified by sex, race and age category, and it shows that the result of the microbiological comparisons were clinically similar for male and female patients, Caucasian and non-Caucasian patients and patients who were 0-12 years, 13-64 years and 65 years or older.

Microbiological Comparison

Treatment	Total	Eradication		Reduction		Persistence		Proliferation	
		N	%	N	%	N	%	N	%
Ciprofloxacin	68	48	70.6	6	8.8	11	16.2	3	4.4
Placebo	72	31	43.1	6	8.3	17	23.6	18	25.0

$p = 0.001$, Cochran-Mantel-Haenszel Rank Score Test

Safety

Ciprofloxacin ointment was evaluated for safety against placebo in 277 patients aged two or older with acute bacterial conjunctivitis. No serious events related to ciprofloxacin ointment or placebo were reported during the study. All adverse events are summarized in Table 19 on Page 8-0206 of NDA 20-369.

No clinically significant difference in visual acuity was observed between ciprofloxacin ointment and placebo. Corrected visual acuity was measured at Study Day 1 (baseline) and each subsequent visit. The maximum change in visual acuity for the worse eye of each patient was calculated as the change in Snellen lines from baseline to the final visit. Data were unavailable for 17 patients receiving ciprofloxacin ointment and 14 patients receiving placebo due to the visual acuity values being non-Snellen data (patients <= 7 years of age) or the lack of visual acuity follow-up data.

Maximum Change in Visual Acuity at Final Visit

Change in Visual Acuity (Snellen Lines)	No Change/ Improvement		One Line Decrease		Two Line Decrease		Greater Than a Two Line Decrease	
	N	%	N	%	N	%	N	%
Ciprofloxacin N=122	109	89.3	9	7.4	3	2.5	1	0.8
Placebo N=124	103	83.1	15	12.1	5	4.0	1	0.8

3. Reviewer's Comment

1. Based on the prespecified analyses plan (Cochran-Mantel-Haenszel test), the reviewer's result is consistent with the sponsor's result on the Physician Impression, microbiological comparison, and the cardinal signs (Discharge, Bulbar Conjunctiva, Erythema, Palpebral Conjunctiva).

2. Since the study was conducted in eight (8) centers, the treatment by site interaction was assessed by the reviewer using an ANOVA model incorporating site effect and treatment by site interaction. Excluding Center 1770 with a single patient, no treatment by center interaction was found in the Physician Impression and the cardinal signs. The type III sum-of-squares and p-values are reported in Table 1 in the appendix.

3. The cardinal signs are 4-point categorical variables ranging from 0 to 3. Although the treatment effects were significant for Discharge and Erythema, the mean differences between the treatment group and the placebo group are less than .2 at Day 3 and Day 4 for all cardinal signs.

III. Study C-91-29

1. Protocol

This is a randomized, double masked, active controlled, and parallel group study conducted in multiple centers. The objective of this study is to compare the clinical and microbiological efficacy and safety for Ciprofloxacin Ophthalmic Ointment against TOBREX in children (ages 2-12) with acute bacterial conjunctivitis. A total of 130 patients (ages 2 -12) will be included in the study with 65 patients included in each treatment group. Patients will 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 am, 3pm, and 9pm) on days 0 and 1; then twice a day while awake (approximately 9 am and 9 pm) on days 2-6.

There are two primary statistical endpoints: Physician Impression at Day 7 over four categories (Cured, Better, Unchanged, and Worse) and comparison of the Day 0 and Day 7 microbiological cultures evaluated over four categories (Eradication, Reduction, Persistence, and Proliferation). Ocular symptoms and signs will also be analyzed. A nonparametric test (rank sum or equivalent) will be used with 5% two sided significance level. Using the results of a previous study, C-87-04/C-87-22, the power to detect a 20% difference in the percentage of patients cured is 80% with the current sample size (65 patients per treatment group). This sample size will be sufficient for both the Physician Impression and the microbiological culture data. The above calculation is based on rank sum test adjusted for ties with 5% two sided significance level.

2. Sponsor's Results

Patients' Evaluability

In Study C-91-29, 9 investigators enrolled a total of 203 patients, using 210 patient numbers (4 patients had both eyes enrolled as separate patient numbers, 1 patient was enrolled twice and 1 patient was enrolled 3 times). One hundred three (103) patient numbers were randomized to Ciprofloxacin and 107 patient numbers were randomized to TOBREX. A total of 61 patients (counted by patient numbers) were non-evaluable for the efficacy and culture positive analyses for the following microbiological reasons:

Patients Excluded from the Culture Positive and Efficacy Analyses			
Reason	Ciprofloxacin	TOBREX	Total
Negative Culture	31	21	52
Invalid Culture (Z1)	3	6	9
Total	34	27	61

Twelve (12) (counted by patient numbers) of the culture positive patients were excluded from the efficacy analyses for the following reasons:

Culture-Positive Patients Excluded from Efficacy Analyses			
Reason	Ciprofloxacin	TOBREX	Total
No Follow-up Culture	2	1	3
Previously Enrolled	0	1	1
Protocol Violation	3	5	8
Total	5	7	12

The remaining 137 evaluable efficacy patients consisted of 65 Ciprofloxacin and 72 TOBREX patients. In this efficacy population, no patient was counted twice.

Demographics

No statistically significant differences were found in demographic characteristics between the treatment groups. The information for sex, age and race for both the intent-to-treat population and the efficacy population is summarized as follows.

Demographic Characteristics of the Efficacy Population

	Sex (p=0.64)		Age (p=0.97)		Race (p=0.66)		
	Male	Female	Mean	Std	Caucasian	Black	Other
Cipro	38	31	4.3	3.04	62	5	2
TOBREX	41	39	4.4	3.02	71	4	5

Demographic Characteristics of the Intent-to-Treat Population

	Sex (p=0.76)		Age (p=0.88)		Race (p=0.81)		
	Male	Female	Mean	Std	Caucasian	Black	Other
Cipro	58	45	4.5	3.19	92	8	3
TOBREX	58	49	4.6	3.21	96	6	5

There were statistically significant differences in baseline erythema ($p<=0.01$) and bulbar conjunctiva ($p=0.04$) between the treatment groups.

Clinical Efficacy

The efficacy results reported here are for the efficacy population only. The results of the intent-to-treat population were consistent with that of the efficacy population.

In the efficacy population all but one patient in each treatment population were either cured or improved on Day 7 in the judgment of the physician. There were no statistically significant differences between the two treatment groups on either Day 3 or 7 ($p = 0.26$, $p = 0.35$, see below). The patients in both treatment groups continued to improve between Days 3 and 7. The 95% confidence limits for the difference between the percentage of Ciprofloxacin patients cured on Day 7 and the percentage of TOBREX patients cured on Day 7 was (-4.4%, 12.4%)

Physician Impression

Day	Treatment	Total	Cured	Improved	Unchanged	Worse
3	Ciprofloxacin	64	28 (43.8%)	35 (54.7%)	0 (0.0%)	1 (1.6%)
	TOBREX	71	38 (53.5%)	32 (45.1%)	1 (1.4%)	0 (0.0%)
7	Ciprofloxacin	64	61 (95.3%)	3 (4.7%)	0 (0.0%)	0 (0.0%)
	TOBREX	69	63 (91.3%)	5 (7.2%)	1 (1.4%)	0 (0.0%)

p = 0.26 (Day 3) and p =0.35 (Day 7), Cochran Mantel Haenszel Rank Score Test

The scores for Discharge/Exudate, Erythema/Swelling and Bulbar Conjunctival Hyperemia were compared between the two treatment groups at each visit. The 95% confidence intervals for the differences between Ciprofloxacin and TOBREX are also given in the following table for each day.

Mean Cardinal Signs for the Efficacy Population at All Visits

Sign	Treat		Day 0	Day 3	Day 7
CONJ-B.	CIPRO	MEAN (Std)	1.5 (0.66)	0.2 (0.42)	0.1 (0.32)
		N	65	64	64
	TOBREX	MEAN (Std)	1.7 (0.57)	0.4 (0.56)	0.1 (0.33)
		N	72	71	69
		95% CI	(-0.4,0.0)	(-0.4,-0.0)	(-0.1,0.1)
		p-value*		0.45	0.90
DISCHARGE	CIPRO	MEAN (Std)	1.8 (0.65)	0.3 (0.44)	0.0 (0.00)
		N	65	64	64
	TOBREX	MEAN (Std)	1.8 (0.62)	0.2 (0.47)	0.0 (0.00)
		N	72	71	69
		95% CI	(-0.2,0.2)	(-0.1,0.3)	(0.0,0.0)¤
		p-value*		0.02	1.0
ERYTHEMA	CIPRO	MEAN (Std)	1.3 (0.63)	0.2 (0.41)	0.1 (0.30)
		N	65	64	64
	TOBREX	MEAN (Std)	1.6 (0.66)	0.2 (0.48)	0.1 (0.35)
		N	72	71	69
		95% CI	(-0.5,-0.1)	(-0.2,0.2)	(-0.1,0.1)
		p-value*		0.45	0.43

* Cochran Mantel Haenszel Rank Score Test for Improvement Relative to Baseline Between Treatments

¤ All Observations Are Zeros

Microbiological Efficacy

For the efficacy population, the bacterial culture change was similar in the two treatment groups (p = 0.63). The 95% confidence interval for the difference between the percentage of Ciprofloxacin patients with a microbiology result of eradication and that of the TOBREX patients was (-9.1%, 14.9%).

Microbiological Comparison

Treatment	Total	Eradication	Reduction	Persistence	Proliferation
Ciprofloxacin	65	56 (86.2%)	1 (1.5%)	7 (10.8%)	1 (1.5%)
TOBREX	72	60 (83.3%)	1 (1.4%)	9 (12.5%)	2 (2.8%)

p = 0.63, Cochran Mantel Haenszel Rank Score Test

Safety

Ciprofloxacin ointment was evaluated for safety against TOBREX in 203 pediatric patients (age<=12). No serious events related to ciprofloxacin ointment or placebo were reported during the study. All adverse events were summarized in Table 31 on Page 8-0762 of NDA 20-369.

Corrected and/or uncorrected visual acuity was measured at Study Day 0 (baseline) and each subsequent visit. If available, corrected visual acuity was used to determine the maximum change in visual acuity. Data were unavailable for 47 patients receiving Ciprofloxacin and 47 patients receiving TOBREX because patients were less than 10 years old, with nonSnellen visual acuity data, or lack of visual acuity follow-up data. No clinically significant difference in visual acuity was observed between Ciprofloxacin and TOBREX.

Maximum Change in Visual Acuity at Final Visit

Change in Visual Acuity (Snellen Lines)	No Change/ Improvement		One Line Decrease		Two Line Decrease		> Two Line Decrease	
	N	%	N	%	N	%	N	%
Ciprofloxacin N=54	49	90.7	2	3.7	2	3.7	1	1.9
TOBREX N=55	50	90.9	2	3.6	3	5.5	0	0

3. Reviewer's Comments

1. Since study C-91-29 was not placebo controlled and bacterial conjunctivitis is a self-limiting disease, it is difficult to tell whether the high cure rates (95.3% for Ciprofloxacin and 91.3% for TOBREX) and high eradication rates (86.2% for Ciprofloxacin and 86.3% for TOBREX) are due to the treatment or the self-limiting property. The cure rates at Day 3 are 43.8% for Ciprofloxacin and 53.5% for TOBREX. The medical officer feels that the Physician Impression at Day 3 is a more appropriate endpoint. The 95% confidence interval for the difference of the cure rates between the treatment groups

(Ciprofloxacin - TOBREX) at Day 3 is (-26.5%, 7.1%). The biomicrological comparison data was not collected at Day 3.

2. The reviewer reanalyzed the cardinal signs by incorporating the baseline score as a covariate into an ANOVA model. The cardinal sign 'Discharge' has value '0', which means 'no discharge', on all subjects at Day 7. The P-values for the differences of cardinal signs between the treatment groups at Day 3 and Day 7 after adjusting by baseline scores are as follows.

P-values of the Treatment Differences (Cipro-TOBREX)

	Erythema	Bulbar Conjunctiva	Discharge
Day 3	0.7268	0.4896	0.5417
Day 7	0.7454	0.7757	1.0000

3. The result of the Physician Impression for the culture negative subset is very close to that for the efficacy population as shown below.

Day	Treatment	Total	Cured	Improved	Unchanged	Worse
3	Ciprofloxacin	28	16 (57.1%)	11 (39.3)	0 (0.0%)	1 (3.6%)
	TOBREX	20	12 (60.0%)	8 (40.0%)	0 (0.0%)	0 (0.0%)
7	Ciprofloxacin	27	26 (96.3%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
	TOBREX	20	18 (90.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)

IV. Study C-88-24

1. Protocol

This is a randomized, double masked, active controlled, and parallel group study conducted in multiple centers. The objective of this study is to compare the clinical and microbiological efficacy and safety for Ciprofloxacin Ophthalmic Ointment against TOBREX in patients with acute bacterial conjunctivitis. A total of 150 patients will be included in the study with 75 patients in each treatment group. Patients will apply a ½" ribbon to the inferior palpebral conjunctiva (cul-de-sac) of the affected eye(s) three times a day while awake (approximately 8 am, 3pm, and 10pm) on days 0 and 1; then twice a day while awake (approximately 8 am and 10 pm) on days 2-6.

There are two primary endpoints: Physician Impression at Day 7 over four categories (Cured, Better, Unchanged, and Worse) and comparison of the Day 0 and Day 7 microbiological cultures evaluated over four categories (Eradication, Reduction, Persistence, and Proliferation). Ocular symptoms and signs will also be analyzed. The primary endpoints will be analyzed by the Wilcoxon test stratified by investigator. Using the results of a previous study, the power to detect a 20% difference in the percentage of patients cured is

80% with the current sample size (75 patients per treatment group). This sample size will be sufficient for both the Physician Impression and the microbiological culture data. The above calculation is based on a two sample binomial test with 5% two sided significance level.

2. Sponsor's Analysis

Patients' Evaluability

A total of 500 patients were enrolled in the study, but three patients withdrew without dosing, leaving 497 patients that were dosed and evaluated for safety. These patients were also evaluated for clinical efficacy in the intent-to-treat population. Among these patients, 178 were culture-positive for bacterial and 319 were not evaluable for efficacy. Among the 319 patients excluded from efficacy analysis, 287 were due to 'negative culture', 11 were due to 'Day 7 missing data', 5 were due to 'Day 7 out of range', 7 were due to 'invalid last instillation time', 8 were due to 'non-compliance' and one was due to 'invalid culture'.

Demographics

No statistically significant differences were found in demographic and baseline characteristics between the treatment groups. The information for sex, age and race for both the intent-to-treat population and the efficacy population is summarized as follows.

Demographic Characteristics of the Efficacy Population

	Sex (p=0.14)		Age (p=0.09)		Race (p=0.92)		
	Male	Female	Mean	Std	Caucasian	Black	Other
Cipro	45	42	45.8	22.9	75	7	5
TOBREX	37	54	51.7	23.1	74	14	3

Demographic Characteristics of the Intent-to-Treat Population

	Sex (p=0.21)		Age (p=0.36)		Race (p=0.60)		
	Male	Female	Mean	Std	Caucasian	Black	Other
Cipro	111	133	44.6	22.2	189	39	16
TOBREX	101	152	46.6	21.8	198	40	13

Clinical Efficacy

The efficacy results reported here are for the efficacy population only. The results of the intent-to-treat population were consistent with that of the efficacy population.

A total of 178 culture-positive patients were included in the analysis of efficacy. The primary parameters in evaluating the clinical efficacy of Ciprofloxacin versus TOBREX were the Physician Impression and clinical cardinal signs. No statistically significant differences were found between the treatments in the Physician Impression.

Physician Impression for Culture-Positive Evaluable Patients

DAY		TOTAL	CURED N	%	BETTER N	%	UNCHANGED N	%	WORSE N	%	p-val
3	TOBREX	42	3	7.1	35	83.3	3	7.1	1	2.4	0.80
	Cipro	39	3	7.7	31	79.5	5	12.8	0	0.0	---
7	TOBREX	91	62	68.1	22	24.2	6	6.6	1	1.1	0.23
	Cipro	87	65	74.7	21	24.1	1	1.1	0	0.0	---

• Cochran-Mantel-Haenszel rank score test

The scores for Discharge/Exudate, Erythema/Swelling and Bulbar Conjunctiva and Palpebral Conjunctiva were compared between the two treatment groups at each visit. For the efficacy population, the overall cardinal signs results at Day 7 are as follows:

Cardinal Signs for Culture-Positive Evaluable Patients

	TOBREX			Cipro			
Sign	N	Mean	Std	N	Mean	Std	P-value
ERYTHEMA	91	0.2	0.39	87	0.1	0.39	0.08
DISCHARGE	91	0.1	0.42	87	0.1	0.25	1.00
CONJ-P.	91	0.2	0.51	87	0.2	0.39	1.00
CONJ-B.	91	0.3	0.56	87	0.2	0.41	0.18

Microbiological Efficacy

A total of 178 patients were culture positive. Ciprofloxacin was significantly more effective than TOBREX for microbiological efficacy (p = 0.01). Ciprofloxacin eradicated or reduced the bacteria in 95.4% of patients (eradicated 85.1%, reduced 10.3%) as compared to 86.8% (eradicated 69.2%, reduced 17.6%) for TOBREX.

Microbiological Efficacy

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

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

Safety

A total of 244 patients in the Ciprofloxacin group and 253 patients in the TOBREX group were evaluated for safety. No serious events related to ciprofloxacin ointment or placebo were reported during the study. All adverse events are reported in Table 26 on Page 8-1261 of NDA 20-369. Visual Acuity data is not available for this study.

3. Reviewer's Comments

1. The reviewer calculated the 95% confidence interval for the difference of cure rates between Ciprofloxacin and TOBREX, which is (-9.1%, 22.3%). The 95% confidence interval for the difference of eradication rates between Ciprofloxacin and TOBREX was also calculated, which is (1.9%, 29.9%).

2. The reviewer reanalyzed the cardinal signs by incorporating the baseline score as a covariate into an ANOVA model. The P-values for the differences of cardinal signs between the treatment groups at Day 7 after adjusting by baseline scores are as follows.

P-values of the Treatment Differences

	Erythema	Bulbar Conjunctiva	Palpebral Conjunctiva	Discharge
Day 7	.6978	.3290	.5471	.4448

3. The result of the Physician Impression for the culture negative subset as shown in the following table is very close to that for the efficacy population.

Day	Treatment	Total	Cured	Improved	Unchanged	Worse
7	TOBREX	139	96 (69.1%)	34 (24.5%)	7 (5.0%)	2 (1.4%)
	Cipro	129	95 (73.6%)	39 (22.5%)	3 (2.3%)	2 (1.6%)

V. Overall Conclusions

1. Study C-93-88 shows that Ciprofloxacin is statistically superior to placebo in both the Physician Impression (p=0.04) and the microbiological culture comparison (p=0.001).

2. Since study C-91-29 was not placebo controlled and bacterial conjunctivitis is a self-limiting disease, it is difficult to tell whether the high cure rates (95.3% for Ciprofloxacin and 91.3% for TOBREX) and high eradication rates (86.2% for Ciprofloxacin and 86.3% for TOBREX) are due to the treatment or the self-limiting property. The cure rates at Day 3 are 43.8% for Ciprofloxacin and 53.5% for TOBREX. The 95% confidence interval for the difference of the cure rates between the treatment groups (Ciprofloxacin - TOBREX) at Day 3 is (-26.5%, 7.1%), which does not show statistical evidence for the equivalence claim of Ciprofloxacin and TOBREX in pediatric patients.

3. Study C-88-24 shows that Ciprofloxacin is not statistically inferior to TOBREX in the Physician Impression (p=0.23, the 95% confidence interval of the difference of cure rates: (-9.1%, 22.3%)) and is statistically superior to TOBREX in the microbiological culture comparison (p=0.01, the 95% confidence interval of the difference of eradication rates: (1.9%, 29.9%)).

4. In both Study C-91-29 and Study C-88-24, the cure rate of the culture negative subset is very similar to that in the efficacy population. The results are listed in the following tables.

Physician Impression at Day 7 (C-91-29)

Efficacy Population

Treatment	Total	Cured	Improved	Unchanged	Worse
Ciprofloxacin	64	61 (95.3%)	3 (4.7%)	0 (0.0%)	0 (0.0%)
TOBREX	69	63 (91.3%)	5 (7.2%)	1 (1.4%)	0 (0.0%)

Culture Negative Subset

Treatment	Total	Cured	Improved	Unchanged	Worse
Ciprofloxacin	27	26 (96.3%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
TOBREX	20	18 (90.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)

Physician Impression at Day 7 (C-88-24)

Efficacy Population

Treatment	Total	Cured	Improved	Unchanged	Worse
TOBREX	91	62 (68.1%)	22 (24.2%)	6 (6.6%)	1 (1.1)
Cipro	87	65 (74.7%)	21 (24.1%)	1 (1.1%)	0 (0.0%)

Culture Negative Subset

Treatment	Total	Cured	Improved	Unchanged	Worse
TOBREX	139	96 (69.1%)	34 (24.5%)	7 (5.0%)	2 (1.4%)
Cipro	129	95 (73.6%)	39 (22.5%)	3 (2.3%)	2 (1.6%)

APPEARS THIS WAY ON ORIGINAL

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CC:

HFD-550/MO/Chambers
HFD-550/Act. Dir./Weintraub
HFD-550/PM/Gorski
HFD-550/Div. File
HFD-340/Div. Sci. Inv.
HFD-725/Lu
HFD-725/Leung
HFD-725/Div. File

Appendix

Table 1. Efficacy Results Adjusted by Site and Treatment by Site Interaction (C-93-88)

Physician Impression

Source	DF	TypeIII SS	Mean Square	Fvalue	Pr>F
TRT	1	2.68401919	2.68401919	8.04	0.0053
INV	6	3.68367257	0.61394543	1.84	0.0965
TRT*INV	6	2.50965354	0.41827559	1.25	0.2838

Discharge

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRT	1	1.88888641	1.88888641	8.26	0.0048
INV	6	4.43948363	0.73991394	3.24	0.0054
TRT*INV	6	2.05594828	0.34265805	1.50	0.1839

Palp Conjunctiva

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRT	1	1.63444586	1.63444586	4.17	0.0433
INV	6	4.21708446	0.70284741	1.79	0.1059
TRT*INV	6	2.15310584	0.35885097	0.92	0.4865

Bulb Conjunctiva

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRT	1	2.36416499	2.36416499	5.21	0.0241
INV	6	2.62999264	0.43833211	0.97	0.4510
TRT*INV	6	2.71774364	0.45295727	1.00	0.4295

Erythema

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRT	1	1.62844020	1.62844020	6.05	0.0152
INV	6	2.75573296	0.45928883	1.71	0.1246
TRT*INV	6	1.38844603	0.23140767	0.86	0.5262