CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-493

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-493
Name of drug:	[redacted] (Gatifloxacin Ophthalmic Solution 0.3%)
Applicant:	Allergan, Inc. 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534
Indication:	Bacterial Conjunctivitis
Documents reviewed:	
Submission:	\\Cdsesub1\n21493\N_000\2002-10-11\clinstat\conjunctivitis
Data:	\\Cdsesub1\n21493\N_000\2002-10-11\crt\datasets
Project manager:	Ms. Lori Gorski
Clinical reviewer:	Jennifer Harris, M.D.
Dates:	Received 5/29/2002
Statistical reviewer:	M. Atiar Rahman, Ph.D.
Statistics team leader:	Stan Lin, Ph.D.
Biometrics division director:	Mohammad Huque

Keywords: NDA review, clinical studies, analysis of variance, Exact Permutation test

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

Considering results from the two submitted studies (#3-01, #3-02) on effects of gatifloxacin in per-protocol population, this reviewer concluded that there was no convincing evidence of significant clinical cure benefit of gatifloxacin over placebo for the treatment of bacterial conjunctivitis in pediatric and adult subjects. Results were borderline significant. There was significant treatment by center interaction, three centers showing results in favor of placebo. However, both studies showed significant benefit of gatifloxacin over placebo with respect to microbiological cure endpoint. A clinical consideration is necessary for making a final decision.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

There were two studies in this submission. The objectives of these studies were to evaluate the efficacy and safety of a 5-day regimen of gatifloxacin in the treatment of acute bacterial conjunctivitis in pediatric and adult patients. The first study (#3-01) was a placebo control study, while the second one (#3-02) was an equivalency study to an active control (ofloxicin). In both of these studies the primary efficacy endpoint was clinical cure in the per-protocol population at Day 6±1. An important secondary efficacy endpoint was microbiological cure at Day 6±1.

1.3 PRINCIPAL FINDINGS

The sponsor's analysis of Study # 3-01 showed that for clinical cure the overall observed difference was18.6% higher in the gatifloxacin group compared to the placebo group. The sponsor's p-value was 0.05. To adjust for the interim analysis, the protocol defined a test level of 0.048 (i.e. α=0.048) for final analysis. Therefore, they did not meet the pre-set significance criteria, but the results were borderline significant. This reviewer's p-value (Exact-p) was 0.056, which was slightly higher but very close to 0.05 or 0.048. Three centers (#121, #125, and #128) showed efficacy in favor of placebo. These three centers contributed about 40% of the total subjects in the trial.

In light of the above discussions, this reviewer concluded that in the submitted data of Study # 3-01 there was no convincing statistically significant evidence of clinical cure in the use of 0.3% Gatifloxacin Ophthalmic Solution. The results were borderline significant. However, data showed statistically significant improvement in the microbiological cure in the gatifloxacin arm compare to placebo.

Sponsor's analysis of Study # 3-02 data showed a 95.2% confidence interval on difference in clinical cure of (-6.7%, 20.1%). The corresponding 95.2% confidence interval in this reviewer's analysis was (-5.4%, 21.7%). Based on reviewer's results and minimum clinical significance difference (delta) of 6%, this reviewer concludes that the submitted data support non-inferiority of gatifloxacin compared to ofloxicin for clinical cure. However, this result needs to be interpreted in the context of assay sensitivity.

Since Study # 3-02 did not have a placebo arm, this reviewer compared the gatifloxacin arm of Study # 3-02 with placebo arm of Study # 3-01. Results of this comparison showed that the gatifloxacin group of Study # 3-02 was statistically significantly different from the observed placebo of Study # 3-01. However, it was not statistically significantly different from the upper 80% confidence limit of placebo of Study # 3-01. From this results this reviewer could not conclude of a

convincing evidence of superiority of gatifloxacin over the placebo of Study #3-301. This reviewer concluded that like Study # 3-01, the result of Study # 3-02 was also borderline significant.

In the presence of treatment by center interaction in the first study and absence of placebo arm in the second study it was difficult to make an overall conclusion of effectiveness of the study drug. This reviewer concluded that none of these studies had convincing statistical evidence of clinical cure benefit of use of gatifloxacin. The results were borderline significant. However, in both studies there was statistically significant improvement in the microbiological cure in the gatifloxacin arm.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

In this NDA the sponsor submitted data to support their claim that the use of Gatifloxacin Ophthalmic Solution 0.3%

2.2 DATA ANALYZED AND SOURCES

In this NDA the sponsor submitted reports of two pivotal Phase 3 studies namely, SPCL-GFLX 3-01 and SPCL-GFLX 3-02. The submission was both in hard copy and electronic. The electronic submission was stored in the Electronic Document Room (EDR) of the Division under this NDA folder. Both of the studies were conducted in USA. The data quality was within acceptable quality.

2.3 STATISTICAL EVALUATION OF EVIDENCE OF EFFICACY / SAFETY

2.3.1 STUDY SPCL-GFLX 3-01

Title: "A Phase III Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of Placebo in the Treatment of Acute Bacterial Conjunctivitis."

2.3.1.1 Design and Objectives

This was a multicenter, double blind, randomized, parallel group study to compare the efficacy and safety of gatifloxacin 0.3% (hereafter referred to as gatifloxacin) with placebo in patients with acute bacterial conjunctivitis. The length of treatment period was 5±1 days. Patients were instructed to instill 1 to 2 drops of study medication to the conjunctival sac of each affected eye approximately every 2 hours (Q2H) while awake for the first two days of study. On Day 1, patients were to receive a minimum of 4 applications per 24 hours, to a maximum of 8 applications per 24 hours. On Day 2, patients were to receive a minimum of 6 applications per 24 hours, to a maximum of 8 applications per 24 hours. For the remainder of the treatment days, patients were instructed to instill medication 4 times daily (QID) approximately every 4 hours (Q4H) while awake. The objectives of the study were as follows:

2.3.1.2 Primary Objectives

The primary objectives of this study were:

- To compare the efficacy of a 5-day regimen (±1 day) of gatifloxacin to the efficacy of a 5-day regimen (±1 day) of placebo in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by resolution of clinical signs of ophthalmic infection assessed on Day 6±1.

- To compare the safety of a 5-day regimen (±1 day) of gatifloxacin to the safety of a 5-day regimen (±1 day) of placebo in the treatment of acute bacterial conjunctivitis in pediatric and adult patients through an analysis of safety based on the incidence of adverse events during treatment.

2.3.1.3 Secondary Objectives

The secondary objectives of this study were:

- To compare the efficacy of gatifloxacin to placebo in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by resolution of clinical signs of ophthalmic infection assessed on Day 3±1.
- To compare the efficacy of gatifloxacin to placebo in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by improvement of signs of ophthalmic infection assessed on Day 3±1 and Day 6±1.
- To compare the efficacy of gatifloxacin to placebo in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by change in severity of each sign and symptom of ophthalmic infection assessed on Day 3±1 and Day 6±1.
- To compare the efficacy of gatifloxacin to placebo in the treatment of acute bacterial conjunctivitis in pediatric and adult patients as evaluated by microbiological assessments of cultures of conjunctival samples taken on Day 3±1 and Day 6±1.

Patients included were male of female ≥ 1 year of age. Patients were randomized in 1:1 ratio to the two treatment groups, stratified by ≤ 12 years and > 12 years. Patients were evaluated at Day 1 (Visit 1= Baseline), Day 3±1, and Day 6±1. Study was carried out in 22 centers in the United States.

2.3.1.4 Patient Enrolment

A total of 265 patients were randomly allocated to study treatment and 93.2% (247/265) of the patients completed the study.

The per protocol (PP) population for this study consisted of all enrolled patients who had a positive bacteriological culture that was above the pathological threshold at baseline and who did not have any significant protocol deviations. Of the 265 patients enrolled in the study, 52 gatifloxacin patients and 48 placebo patients were included in the PP population.

The modified intent to treat (mITT) population consisted of all enrolled patients who received study drug and had at least one post baseline efficacy measure. Of the 265 patients enrolled in the study, 133 gatifloxacin patients and 128 placebo patients were included in the mITT group.

2.3.1.5 Efficacy Assessment and Endpoints

The affected eye(s) were cultured at the baseline visit and a reference eye was determined for each patient. If both eyes were culture positive or culture negative, then the right eye became the reference eye. If only one of the affected eyes was culture positive, then that eye became the reference eye. Data from the reference eye were used in the efficacy analyses. Data from all treated eyes were included in the safety analyses.

At each visit, the severity of each sign and symptom was rated on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Clinical signs included mucopurulent discharge and bulbar conjunctival erythema, and clinical symptoms included ocular discomfort (including foreign body sensation and/or itching and/or photophobia), and tearing.

The primary efficacy endpoint was clinical cure in the PP population at Day 6±1. A clinical cure was achieved when the scores for the 2 clinical signs of ophthalmic infection (mucopurulent discharge and bulbar conjunctival erythema) were equal to 0 = none.

Secondary efficacy endpoints were clinical cure at Day 3±1; clinical improvement at Day 3±1 and Day 6±1 (achieved if the average score for the 2 signs was ≤ 1.5 with each score < 3 and not greater than baseline); microbiological cure at Day 3±1 and Day 6±1 (achieved when all pathogens above threshold in the baseline culture were eradicated); changes from baseline in the severity of clinical signs and symptoms (ocular discomfort and tearing) at Day 3±1 and Day 6±1.

The microbial response of the reference eye was determined by culture of conjunctival swab samples collected at each visit. Response was categorized as eradication, reduction, persistence, or proliferation.

2.3.1.6 Disposition of Patients, Demography, and Baseline Disease Conditions

The summary of patient's disposition, from sponsor's report, is given in Table 1A and Table 1B in the appendix for Safety and Modified Intent-to-Treat Population, respectively. The summary of patient's baseline characteristics, from sponsor's report, is given in Table 2 in the appendix for Safety Population.

A total of 265 patients were randomly allocated to study treatment and 93.2% (247/265) of patients completed the study. The percentage of patients in the safety population completing the study was comparable between treatment groups: 91.8% (123/134) of gatifloxacin patients versus 94.7% (124/131) of placebo patients. Similarly, the percent of patients in the mITT population completing the study was comparable between treatment groups: 94.0% (125/133) of gatifloxacin patients versus 95.3% (122/128) of placebo patients. By definition, all patients in the PP population completed the study.

The primary reasons for patient discontinuation in the safety population were as follows:

- treatment failure: 1.5% (2/134) of gatifloxacin and 2.3% (3/131) of placebo patients
- adverse events: 2.2% (3/134) of gatifloxacin and 0.8% (1/131) of placebo patients
- consent withdrawn: 2.2% (3/134) of gatifloxacin and 0.8% (1/131) of placebo patients

The sponsor concluded that there were no statistically significant between-group differences in demographic or baseline characteristics in the safety population. The mean age was 38.4 years, ranging from 1 to 90 years, and 18.9% (50/265) of patients were ≤ 12 years old. Overall, 65.3% (173/265) of patients were female and 34.7% (92/265) of patients were male. The majority of patients were Caucasian, 80.8% (214/265). Iris color was equally represented, with dark-colored irises (brown) noted in 50.6% (134/265) of patients and light-colored irises (blue, green, other) noted in 49.4% (131/265) of patients. The mean duration of the current episode of conjunctivitis prior to treatment was 1.7 days in the safety population, ranging from 0 to 8 days.

2.3.1.7 Sponsor's Analysis of Baseline Data

Analyses of baseline data were performed on the PP and Safety populations. Summary statistics were calculated by treatment group for each continuous variable. Between-group differences for continuous variables were tested using an F test from an analysis of variance (ANOVA) model or a Wilcoxon rank-sum test. Categorical variables were summarized by number and percent for each treatment group and compared between treatments using the Fisher exact test with the following exceptions: the Wilcoxon rank-sum test was used to compare the severity of ophthalmic signs, and no statistical comparisons were performed for medical history, baseline organisms above pathological threshold, and previous medications.

2.3.1.8 Sponsor's Analysis of Primary Efficacy Data

Clinical cure success rates at Day 6±1 were compared between treatments using a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by age group (≤ 12 years and > 12 years). This analysis was pre-defined in the protocol. In addition, a 2-sided confidence interval (CI) for the gatifloxacin – placebo difference in success rates was calculated based on a Z-test procedure. To account for the interim analysis, the CMH test significance level for the final analysis was set to 0.048 and the CI level was set to 95.2%. Between-group comparisons per investigator utilized a 2-sided Fisher exact test and a 2-sided 95% CI for the difference in success rates. Treatment-by-investigator site and treatment-by-age group interactions were assessed independently using the Breslow-Day test at the 0.10 significance level.

2.3.1.9 Sponsor's Analysis of Secondary Efficacy Data

Clinical cure on Day 3±1, clinical improvement on Day 3±1 and Day 6±1, and microbiological cure on Day 3±1 and Day 6±1 were analyzed as described above for the primary efficacy variable. However, 2-sided 95% CIs were calculated rather than 95.2%.

Changes from baseline in the severity of the individual ophthalmic signs (mucopurulent discharge and bulbar conjunctival erythema) and symptoms (ocular discomfort and tearing) for the reference eye were summarized by visit. Between-group comparisons of the mean change from baseline utilized Van Elteren tests stratified by age group.

The culture classifications were compared between treatment groups using a Van Elteren test stratified for age group. For this analysis, microbial response was rated as 0 = eradication, 1 = reduction, 2 = persistence, or 3 = proliferation. The response analyzed for each patient was the worst (highest) response (0 to 3) over all pathogens present above pathological threshold at baseline.

Microbiological response was also summarized by organism; however no statistical comparisons between treatment groups were conducted.

2.3.1.10 Sponsor's Analysis of Safety Data

All safety analyses were conducted on the safety population. All reported adverse events were coded from the verbatim text into preferred terms and grouped by system organ class using the Medical Dictionary for Regulatory Activities (MedDRA), version 2.4. At each level of summarization (global, system organ class, and preferred term), a patient was counted once if he/she reported one or more experiences at that level. The treatment groups were compared at each level of summarization using Fisher exact tests for all adverse events regardless of causality, for treatment-related adverse events, and for serious adverse events.

2.3.1.11 Reviewer's Analysis of Efficacy Data

The sponsor's CMH test was based on the normal approximation i.e. z-test. Therefore, the p-values and the confidence intervals are not exact. This reviewer reanalyzed the efficacy data using the exact test stratified by age group (≤ 12 years and > 12 years). This test gives the exact p-values. This reviewer performed this analysis to check the robustness of normal approximation results.

2.3.2 SPONSOR'S RESULTS AND CONCLUSIONS

Following are the results of sponsor's analyses of primary and secondary efficacy endpoints.

2.3.2.1 Clinical Cure

The primary efficacy endpoint was the clinical cure success rate in the PP population at Day 6±1. Clinical cure success was achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema were equal to 0 (none). Clinical cure rates in the reference eye for the per-protocol population from the sponsor's calculations are shown in Text Table 1.

Text Table 1: Summary of Clinical Cure in the Reference Eye, Study 3-01

(Per Protocol Population)

	Clinical Cure[a]	Gatifloxacin N = 52	Placebo N = 48	P-value[b]	Difference	CI[c]
Day 3		N = 45	N = 42			
	Success	9 (20.0%)	6 (14.3%)	0.573	5.7	(-10.1, 21.5)
	Failure	36 (80.0%)	36 (85.7%)			
Day 6		N = 52	N = 48			
	Success	40 (76.9%)	28 (58.3%)	0.050	18.6	(0.4, 36.8)
	Failure	12 (23.1%)	20 (41.7%)			

Source: Section 14.2, Table 1

a clinical cure success if mucopurulent discharge and bulbar conjunctival erythema scored as 0 = none

b P-value from Cochran-Mantel-Haenszel test stratified for age group (≤12 years and > 12 years)

c gatifloxacin – placebo difference in success rates and confidence interval (CI) based on Z test; confidence levels were 95% for Day 3 and 95.2% for Day 6

Source Table 11.4.1.1 of Sponsor's Analysis

At Day 6, the success rate was 18.6% higher with gatifloxacin than with placebo. The statistical test result of p = 0.050 was not significant because the final significance level was set at 0.048 to account for the interim analysis. Based on a 95.2% confidence interval procedure, the lower limit was strictly greater than 0. The sponsor concluded that this indicates a statistically significant difference in favor of gatifloxacin over placebo.

Reviewer's comment: Sponsor's pre-defined primary analysis CMH test showed p=0.05. The sponsor's significance level was α=0.048. Therefore, according to the sponsor's criteria the result was not statistically significant. The lower limit of the 95.2% CI was away from zero by a very small margin, indicating statistically significant difference. This was contradictory. A possible source of this contradiction could be the use the normal approximation. At best this result could be considered as borderline significant.

2.3.2.2 Microbiological Cure

A microbiological cure was achieved when all pathogens above the pathological threshold in the conjunctival swab sample at baseline were eradicated. Microbiological cure rates in the reference eye for the PP population is shown in Text Table 2.

Text Table 2: Summary of Microbiological Cure in the Reference Eye, Study 3-01 (Per Protocol Population)

Microbiological Cure[a]	Gatifloxacin N = 52	Placebo N = 48	P-value[b]	Difference	95% CI[c]
Day 3	N = 44	N = 41			
Success	39 (88.6%)	20 (48.8%)	< 0.0001	39.9	(21.9, 57.8)
Failure	5 (11.4%)	21 (51.2%)			
Day 6	N = 52	N = 47			
Success	48 (92.3%)	34 (72.3%)	0.009	20.0	(5.1, 34.8)
Failure	4 (7.7%)	13 (27.7%)			

Source: Section 14.2, Table 3

a microbiological cure success if all pathogens above threshold at baseline were eradicated

b P-value from Cochran-Mantel-Haenszel test stratified for age group (≤12 years and > 12 years)

c gatifloxacin – placebo difference in success rates and 95% confidence interval (CI) based on Z test

(Source Table 11.4.1.2 of Sponsor's Analysis)

The sponsor concluded that microbiological cure with gatifloxacin was evident by Day 3 when the success rate was 39.9% higher with gatifloxacin than with placebo, representing both a clinically and statistically significant difference. At Day 6, the eradication rate was 20.0% higher with gatifloxacin than with placebo, again a clinically and statistically significant difference.

2.3.2.3 Center by drug interaction

The study was conducted at 22 investigator sites; 18 sites contributed to the PP population.

Clinical cure success rates at day 6 for each investigator site were as follows:

Text Table 3: Clinical Cure Success Rates at Day 6[a] per Investigator Site, Study 3-01 (Per Protocol Population)

Investigator Site	Gatifloxacin N = 52	Placebo N = 48
101	1/2 (50.0%)	0
103	3/3 (100.0%)	1/2 (50.0%)
108	0	2/3 (66.7%)
111	1/1 (100.0%)	0
116	1/1 (100.0%)	0/1 (0%)
117	3/3 (100.0%)	0/4 (0%)
118	2/3 (66.7%)	2/3 (66.7%)
119	1/4 (25.0%)	1/6 (16.7%)
121	**5/8 (62.5%)**	**9/10 (90.0%)**
123	1/2 (50.0%)	0
125	**4/6 (66.7%)**	**3/3 (100.0%)**
128	**9/10 (90.0%)**	**3/3 (100.0%)**
129	1/1 (100.0%)	1/3 (33.3%)
131	5/5 (100.0%)	2/4 (50.0%)
136	0	2/2 (100.0%)
138	0	0/1 (0%)
144	1/1 (100.0%)	2/2 (100.0%)
149	2/2 (100.0%)	0/1 (0%)

a clinical cure success if mucopurulent discharge and bulbar conjunctival erythema scored as 0 = none
b gatifloxacin – placebo difference in clinical cure success rates
(Source Table 11.4.2.4-1 of Sponsor's Analysis)

The sponsor noted that while many of the sites had small samples and the success rates varied, the majority favored gatifloxacin over placebo. The treatment-by-investigator site interaction was statistically significant, p = 0.034. The sponsor performed a sensitivity analysis to investigate the observed treatment-by-investigator site interaction by removing each of the 3 investigator sites (121, 125, and 128) where the clinical cure success rate with placebo was greater than with gatifloxacin. The following table summarizes the results of these analyses.

Text Table 4: Clinical Cure Success Rates at Day 6[a] Excluding Sites where the Success Rate was Higher with Placebo, Study 3-01 (Per-Protocol Population)

Analysis Population	Clinical Cure Success at Day 6[a] Gatifloxacin	Placebo	Difference[b]	Treatment P-value[c]	Interaction P-value[d]
PP all sites	40/52 (76.9%)	28/48 (58.3%)	18.6%	0.050	0.034
exclude site 121	35/44 (79.5%)	19/38 (50.0%)	29.5%	0.005	0.121
exclude site 125	36/46 (78.3%)	25/45 (55.6%)	22.7%	0.023	0.045
exclude site 128	31/42 (73.8%)	25/45 (55.6%)	18.3%	0.082	0.026

a clinical cure success if mucopurulent discharge and bulbar conjunctival erythema scored as 0 = none
b gatifloxacin – placebo difference in clinical cure success rates
c P-value from Cochran-Mantel-Haenszel test stratified for age group (≤12 years and > 12 years)
d P-value from Breslow-Day test for treatment-by-investigator site interaction
(Source: Table 11.4.2.4-2 of Sponsor's Analysis)

These analyses indicated that investigator site 121 was the potential cause of the significant interaction, for by its exclusion, the treatment-by-site interaction term was non-significant at the p = 0.10 level. Investigator sites 125 and 128 did not seem to have contributed to the interaction. This

was possibly due to the small sample size in the placebo group at each site whose cure rate estimate of 100% was not a reliable measure.

The sponsor reviewed the demographics and baseline characteristics of the PP population for site 121 for possible explanations of the observed difference in clinical success rates. In general, site 121 was similar to other study sites in terms of sex, race, iris color, number of organisms above threshold at baseline, reference eye, and duration of current episode. Two notable differences were that the PP population at site 121 included only patients > 12 years of age and only patients with unilateral infections.

Therefore, clinical cure success rates in the PP population were analyzed by age group and location of baseline infection, and are summarized in the following table:

Text Table 5: Clinical Cure Success Rates at Day 6[a] by Age and Infection Subgroups with and without Site 121, Study 3-01 (Per-Protocol Population)

		All Sites		Investigator Site 121		All Sites Excluding 121	
Baseline Variable	**Category**	**Gatiflox (N = 52)**	**Placebo (N = 48)**	**Gatiflox (N = 8)**	**Placebo (N = 10)**	**Gatiflox (N = 44)**	**Placebo (N = 38)**
Age group	≤ 12 years	13/14 (92.9%)	7/12 (58.3%)	0	0	13/14 (92.9%)	7/12 (58.3%)
	> 12 – < 65 years	18/26 (69.2%)	16/28 (57.1%)	2/4 (50.0%)	5/5 (100%)	16/22 (72.7%)	11/23 (47.8%)
	≥ 65 years	9/12 (75.0%)	5/8 (62.5%)	3/4 (75.0%)	4/5 (80.0%)	6/8 (75.0%)	1/3 (33.3%)
Infection	unilateral	22/29 (75.9%)	17/26 (65.4%)	5/8 (62.5%)	9/10 (90.0%)	17/21 (81.0%)	8/16 (50.0%)
	bilateral	18/23 (78.3%)	11/22 (50.0%)	0	0	18/23 (78.3%)	11/22 (50.0%)

Source: Section 14.5, Tables 19.9, 28 and 29
a clinical cure success if mucopurulent discharge and bulbar conjunctival erythema scored as 0 = none
Source: Table 11.4.2.4-4 of Sponsor's Analysis

These analyses indicated that across all sites, gatifloxacin-treated patients had a higher rate of clinical success than placebo-treated patients did in each of the 3 age subgroups of the PP population. Patients in the youngest subgroup (≤ 12 years) showed the greatest benefit from gatifloxacin. However as gatifloxacin was also effective in older patients, the lack of younger patients at investigator site 121 would not explain why the overall treatment effect was reversed at that center.

These analyses also indicated that across all sites, gatifloxacin-treated patients had a higher rate of clinical success than placebo-treated patients did in both unilateral and bilateral infection subgroups of the PP population . Similarly, there was no difference in the effectiveness of gatifloxacin between the 2 infection subgroups across all patients excluding site 121. Thus the lack of bilateral patients at investigator site 121 would not explain why the overall treatment effect was reversed at that center.

2.3.3 REVIEWER'S FINDINGS AND CONCLUSIONS

2.3.3.1 Clinical and Microbiological Cure

The following are the results of this reviewer's analysis based on the exact test.

Text Table 6: Summary of Clinical and Microbiological Cure in the Reference Eye, Study 3-01 (Reviewer's Table)

Endpoint	Population	Drug Assignment	Outcome		P-value
			Gatiflox.	Placebo	
Clinical cure	All randomized	Actual assignment	84/134	73/131	0.2614
	Modified ITT	"	84/131	73/130	0.2056
	Per-Protocol	"	40/52	28/48	0.0560
	All randomized	ITT assignment	85/135	72/130	0.2128
	Modified ITT	"	85/132	72/129	0.1644
	Per-Protocol	"	40/52	28/48	0.0560
Microbiological cure	All randomized	Actual assignment	57/72	38/62	0.0350
	Modified ITT	"	57/69	38/61	0.0107
	Per-Protocol	"	47/52	33/48	0.0116
	All randomized	ITT assignment	57/73	38/61	0.0570
	Modified ITT	"	57/70	38/60	0.0289
	Per-Protocol	"	47/52	33/48	0.0116

Reviewer's analysis showed that the difference in clinical cure between gatifloxacin and placebo was not statistically significant in ITT or per-protocol population. The difference in microbiological cure between gatifloxacin and placebo in both ITT and per-protocol population was statistically significant.

2.3.3.2 Reviewer's conclusion of Study 3-01

For clinical cure the overall observed difference was 18.6% higher in the gatifloxacin group compared to the placebo group. The sponsor's p-value was 0.05. To adjust for the interim analysis, the protocol defined a test level of 0.048 (i.e. α=0.048) for final analysis. The sponsor did not meet the pre-set significance criteria. However, results were borderline significant. This reviewer's p-value (Exact-p) was 0.056, which was slightly higher but very close to 0.05 or 0.048. There were three centers (#121, #125, and #128) which showed qualitative interactions i.e. efficacy in favor of placebo. These three centers contributed about 40% of the total subjects in the trial.

In light of the above discussions, this reviewer concludes that in the submitted data there is no convincing statistically significant evidence of clinical cure in the use of 0.3% Gatifloxacin Ophthalmic Solution. There was statistically significant improvement in the microbiological cure in the gatifloxacin arm compare to placebo.

2.3.4 STUDY SPCL-GFLX 3-02

Title: "A Phase III Multicenter, Randomized, Double-Masked, Parallel Study to Compare the Safety and Efficacy of 0.3% Gatifloxacin Ophthalmic Solution with that of 0.3% Ofloxacin Ophthalmic Solution in the Treatment of Acute Bacterial Conjunctivitis"

2.3.4.1 Design and Objectives

This was a multicenter, double blind, randomized, parallel group study to compare the efficacy and safety of gatifloxacin 0.3% (hereafter referred to as gatifloxacin) with those of ofloxacin 0.3% ophthalmic solution (hereafter referred to as ofloxacin) in patients with acute bacterial conjunctivitis. The goal of this study was to demonstrate that gatifloxacin 0.3% ophthalmic solution was at least as effective as ofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis in patients ≥ 1 year of age. The length of treatment period was 5±1 days. Patients were instructed to instill 1 to 2 drops of study medication to the conjunctival sac of each affected eye approximately every 2 hours (Q2H) while awake for the first two days of study, and then 4 times daily while awake on days 3 to 5±1. On day 1, patients were to receive a minimum of 4 applications per 24 hours, to a maximum of 8 applications per 24 hours. On day 2, patients were to receive a minimum of 6 applications per 24 hours, to a maximum of 8 applications per 24 hours. For the remainder of the treatment days, patients were instructed to instill medication 4 times daily (QID) approximately every 4 hours (Q4H) while awake. The objectives of the study were as follows:

2.3.4.2 Primary Objectives

The primary objectives of this study were:

- To compare the efficacy of a 5-day regimen (±1 day) of gatifloxacin to the efficacy of a 5-day regimen (±1 day) of ofloxacin in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by resolution of clinical signs of ophthalmic infection assessed on Day 6±1.

- To compare the safety of a 5-day regimen (±1 day) of gatifloxacin to the safety of a 5-day regimen (±1 day) of ofloxacin in the treatment of acute bacterial conjunctivitis in pediatric and adult patients, when safety was analyzed based on the incidence of adverse events (AEs) during treatment.

2.3.4.3 Secondary Objectives

The secondary objectives of this study were:

- To compare the efficacy of gatifloxacin to the efficacy of ofloxacin in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by resolution of clinical signs of ophthalmic infection assessed on Day 3±1.
- To compare the efficacy of gatifloxacin to the efficacy of ofloxacin in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by improvement of signs of ophthalmic infection assessed on Day 3±1 and Day 6±1.

- To compare the efficacy of gatifloxacin to the efficacy of ofloxacin in the treatment of acute bacterial conjunctivitis in pediatric and adult patients when measured by change in severity of each sign and symptom of ophthalmic infection assessed on Day 3±1 and Day 6±1.

- To compare the efficacy of gatifloxacin to the efficacy of ofloxacin in the treatment of acute bacterial conjunctivitis in pediatric and adult patients as evaluated by microbiological assessments of conjunctival samples taken on Day 3±1 and Day 6±1.

Patients included were male of female ≥ 1 year of age. Patients were randomized in 1:1 ratio to the two treatment groups, stratified by ≤ 12 years and > 12 years. Patients were evaluated Day 1 (Visit 1= Baseline), Day 3±1, and Day 6±1. Study was carried out in 31 centers in the United States.

2.3.4.4 Patient Enrolment

A total of 459 patients were randomly allocated to study treatment and 94.8% (435/459) of patients completed the study.

The per protocol (PP) population for this study consisted of all enrolled patients who had a positive bacteriological culture that was above the pathological threshold at baseline and who did not have any significant protocol deviations. Of the 459 patients enrolled in the study, 78 gatifloxacin patients and 69 ofloxacin patients were included in the PP population.

The modified intent to treat (mITT) population consisted of all enrolled patients who received study drug and had at least one post baseline efficacy measure. Of the 459 patients enrolled in the study, 220 patients were included in the gatifloxacin mITT group and 222 patients were included in the ofloxacin mITT group.

2.3.4.5 Efficacy assessment and endpoints

The affected eye(s) were cultured at the baseline visit and a reference eye was determined for each patient. If both eyes were culture positive or culture negative, then the right eye became the reference eye. If only one of the affected eyes was culture positive, then that eye became the reference eye. Data from the reference eye were used in the efficacy analyses. Data from all treated eyes were included in the safety analyses.

At each visit, the severity of each sign and symptom was rated on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Clinical signs included mucopurulent discharge and bulbar conjunctival erythema, and clinical symptoms included ocular discomfort (including foreign body sensation and/or itching and/or photophobia), and tearing.

The primary efficacy endpoint was clinical cure in the PP population at Day 6±1. A clinical cure was achieved when the scores for the 2 clinical signs of ophthalmic infection (mucopurulent discharge and bulbar conjunctival erythema) were equal to 0 = none.

Secondary efficacy endpoints were clinical cure at Day 3±1; clinical improvement at Day 3±1 and Day 6±1 (achieved if the average score for the 2 signs was ≤ 1.5 with each score < 3 and not greater than baseline); microbiological cure at Day 3±1 and Day 6±1 (achieved when all pathogens above threshold in the baseline culture were eradicated); changes from baseline in the severity of clinical signs and symptoms (ocular discomfort and tearing) at Day 3±1 and Day 6±1.

The microbial response of the reference eye was determined by culture of conjunctival swab samples collected at each visit. Response was categorized as eradication, reduction, persistence, or proliferation.

2.3.4.6 Disposition of Patients, Demography, and Baseline Disease Conditions

The summary of patient's disposition, from sponsor's report, is given in Table 3A and Table 3B in the appendix for Safety and Modified Intent-to-Treat Population, respectively. The summary of patient's baseline characteristics, from sponsor's report, is given in Table 4 in the appendix for Safety Population.

A total of 459 patients were enrolled and 94.8% (435/459) of patients completed the study. The percentage of patients in the safety population completing the study was comparable between treatment groups: 95.7% (220/230) of gatifloxacin patients versus 93.9% (215/229) of ofloxacin patients. Similarly, the percentage of patients in the mITT population completing the study was comparable between treatment groups: 97.3% (214/220) of gatifloxacin patients versus 95.0% (211/222) of ofloxacin patients. By definition, all patients in the PP population completed the study.

The primary reasons for patient discontinuation in the safety population were as follows:

- lost to follow-up: 2.2% (5/230) of gatifloxacin and 2.6% (6/229) of ofloxacin patients
- adverse events: 1.3% (3/230) of gatifloxacin and 2.6% (6/229) of ofloxacin patients
- protocol violation: 0.4% (1/230) of gatifloxacin and 0 ofloxacin patients
- did not meet inclusion criteria: 0.4% (1/230) of gatifloxacin and 0 ofloxacin patients
- other: 0 gatifloxacin patients and 0.9% (2/229) of ofloxacin patients

The sponsor concluded that there were no statistically significant between-group differences in demographic or baseline characteristics in the safety population. The mean age was 39.3 years, ranging from 1 to 99 years, and 16.1% (74/459) of patients were ≤ 12 years old. Overall, 63.0% (289/459) of patients were female and 37.0% (170/459) of patients were male. The majority of patients were Caucasian, 69.7% (320/459). Iris color was equally represented, with dark-colored irises (brown) noted in 51.6% (237/459) of patients and light-colored irises (blue, green, other) noted in 48.4% (222/459) of patients. The mean duration of the current episode of conjunctivitis prior to treatment was 1.5 days in the safety population, ranging from 0 to 4 days.

2.3.4.7 Sponsor's Analysis of Baseline Data

Analyses of baseline data were performed on the PP and Safety populations. Summary statistics were calculated by treatment group for each continuous variable. Between-group differences for continuous variables were tested using an F test from an analysis of variance (ANOVA) model or a Wilcoxon rank-sum test. Categorical variables were summarized by number and percent for each treatment group and compared between treatments using the Fisher exact test with the following exceptions: the Wilcoxon rank-sum test was used to compare the severity of ophthalmic signs, and no statistical comparisons were performed for medical history, baseline organisms above pathological threshold, and previous medications.

2.3.4.8 Sponsor's Analysis of Primary Efficacy Data

To compare treatments for the primary efficacy endpoint (clinical cure at Day 6±1), a 2-sided confidence interval (CI) for the gatifloxacin – ofloxacin difference in success rates was calculated. To account for one interim analysis, the CI level was 95.2%. The equivalence limits governing the comparison were ±20%, based on the success rate of < 80% in the ofloxacin group. Gatifloxacin was to be declared equivalent to the active control ofloxacin if the CI fell within the range -20% to +20%. Gatifloxacin was to be declared non-inferior to ofloxacin if the lower limit of the CI was greater than -20%. Gatifloxacin was to be declared superior to ofloxacin if the lower limit of the CI exceeded 0.

For descriptive purposes, a 2-sided test of the difference in success rates was conducted using a Cochran-Mantel Haenszel (CMH) test stratified by the age group (≤ 12 years and > 12 years). Treatment-by-investigator site, and treatment-by-age group interactions were assessed independently using the Breslow-Day test at the 0.10 significance level. For each investigator site, a 2-sided 95% CI for the gatifloxacin – ofloxacin difference in success rates was calculated. For descriptive purposes, 2-sided tests of the difference in the clinical cure success rates between treatments at each visit were conducted using the Fisher exact test.

2.3.4.9 Sponsor's Analysis of Secondary Efficacy Data

Clinical cure on Day 3±1, clinical improvement on Day 3±1 and Day 6±1, and microbiological cure on Day 3±1 and Day 6±1 were analyzed as described above for the primary efficacy variable; however the CI levels were 95% rather than 95.2%.

Changes from baseline in the severity of the individual ophthalmic signs (mucopurulent discharge and bulbar conjunctival erythema) and symptoms (ocular discomfort and tearing) for the reference eye were summarized by visit. Between-group comparisons of the mean change from baseline utilized Van Elteren tests, stratified by age group. In addition, a distribution-free 2-sided 95% CI for the gatifloxacin – ofloxacin difference in change from baseline was calculated (Hollander and Wolfe, 1973). P-values and CIs were provided as descriptive statistics since equivalence limits governing the comparisons were not established.

The microbiological responses of the reference eye were compared between treatment groups using a Van Elteren test stratified for age group. In addition, a distribution-free 2-sided 95% CI for the shift in location between the 2 treatment groups was calculated. For these analyses, microbial response was rated as 0 = eradication, 1 = reduction, 2 = persistence, or 3 = proliferation. The response analyzed for each patient was the worst (highest) response (0 to 3) over all pathogens present above pathological threshold at baseline. Microbiological response was also summarized by organism; however no statistical comparisons between treatment groups were conducted.

2.3.4.10 Sponsor's Analysis of Safety Data

All safety analyses were conducted on the safety population. All reported adverse events were coded from the verbatim text into preferred terms and grouped by system organ class using the Medical Dictionary for Regulatory Activities (MedDRA), version 2.4. At each level of summarization (global, system organ class, and preferred term), a patient was counted once if he/she reported one or more experiences at that level. The treatment groups were compared at each level of summarization using

Fisher exact tests for all adverse events regardless of causality, for treatment-related adverse events, and for serious adverse events.

2.3.4.11 Reviewer's Analysis of Efficacy Data

The sponsor's CMH test was based on the normal approximation i.e. z-test. Therefore, the p-values and the confidence intervals are not exact. This reviewer reanalyzed the efficacy data using the permutation test stratified by age group (≤ 12 years and > 12 years). This test gives the exact p-values. Also the exact 95.2% confidence intervals were calculated on the difference of proportions. This reviewer performed this analysis to check the robustness of normal approximation results.

2.3.5 SPONSOR'S RESULTS AND CONCLUSIONS

Following are the results of sponsor's analyses of primary and secondary efficacy endpoints.

2.3.5.1 Clinical Cure

The primary efficacy endpoint was the clinical cure success rate in the PP population at Day 6±1. Clinical cure success was achieved when the scores for mucopurulent discharge and bulbar conjunctival erythema were equal to 0 (none). Clinical cure rates in the reference eye for the PP population from the sponsor's calculations is shown in Text Table 7.

Text Table 7: Summary of Clinical Cure in the Reference Eye, Study 3-02

(Per-Protocol Population)

	Clinical Cure[a]	Gatifloxacin N = 78	Ofloxacin N = 69	P-value[b]	Difference	CI[c]
Day 3		N = 73	N = 66			
	Success	12 (16.4%)	16 (24.2%)	0.208	-7.8	(-21.2, 5.6)
	Failure	61 (83.6%)	50 (75.8%)			
Day 6		N = 78	N = 69			
	Success	64 (82.1%)	52 (75.4%)	0.325	6.7	(-6.7, 20.1)
	Failure	14 (17.9%)	17 (24.6%)			

Source: Section 14.2, Table 1

a clinical cure success if mucopurulent discharge and bulbar conjunctival erythema scored as 0 = none

b P-value from Cochran-Mantel-Haenszel test stratified for age group (≤12 years and > 12 years)

c gatifloxacin – ofloxacin difference in success rates and confidence interval (CI) based on Z test; CI levels were 95% for Day 3 and 95.2% for Day 6

Source Table 11.4.1.1 of Sponsor's Analysis

At Day 6, the success rate was 6.7% higher with gatifloxacin than with ofloxacin and the 95.2% CI ranged from -6.7% to +20.1% (Section 14.2, Table 1). Thus gatifloxacin was shown to be at least clinically equivalent and statistically non-inferior to the active control ofloxacin.

2.3.5.2 Microbiological Cure

A microbiological cure was achieved when all pathogens above the pathological threshold in the conjunctival swab sample at baseline were eradicated. Microbiological cure rates in the reference eye for the PP population is shown in Text Table 8.

Text Table 8: Summary of Microbiological Cure in the Reference Eye, Study 3-02 (Per-Protocol Population)

Microbiological Cure[a]	Gatifloxacin N = 78	Ofloxacin N = 69	P-value[b]	Difference	95% CI[c]
Day 3	N = 73	N = 66			
Success	60 (82.2%)	53 (80.3%)	0.767	0.019	0.019
Failure	13 (17.8%)	13 (19.7%)		(-0.111, 0.149)	(-0.111, 0.149)
Day 6	N = 78	N = 68			
Success	65 (83.3%)	58 (85.3%)	0.753	-0.020	-0.020
Failure	13 (16.7%)	10 (14.7%)		(-0.139, 0.099)	(-0.139, 0.099)

Source: Section 14.2, Table 3
a microbiological cure success if all pathogens above threshold at baseline are eradicated
b P-value from Cochran-Mantel-Haenszel test stratified for age group (≤12 years and > 12 years)
c gatifloxacin – ofloxacin difference in success rates and 95% confidence interval (CI) based on Z test
Source Table 11.4.1.2 of Sponsor's Analysis

Microbiological cure was established by Day 3 for both gatifloxacin and ofloxacin, with success rates of 82.2% and 80.3%, respectively (Section 14.2, Table 3). At Day 6, the cure rates were 83.3% and 85.3%, respectively. There were no clinically or statistically significant differences between the two treatment groups.

2.3.5.3 Center by Drug interaction

The study was conducted at 31 investigator sites; 25 sites contributed patients to the analysis of the PP population. The treatment-by-investigator site interaction was not statistically significant in either the PP population (p = 0.172) or mITT population, p = 0.923.

2.3.6 REVIEWER'S FINDINGS AND CONCLUSIONS

2.3.6.1 Clinical and Microbiological Cure

The following are the results of this reviewer's analysis based on the exact test.

Text Table 9: Summary of Clinical and Microbiological Cure in the Reference Eye, Study 3-02 (Reviewer's Table)

Endpoint	Population	Drug Assignment	Outcome Gatiflox.	Outcome Oflox.	P-value	95.2% C.I. On difference* (Gatiflox. - Oflox.)
Clinical cure	All randomized	Actual assignment	173/230	154/229	0.0612	– 0.42 , 16.37
	Modified ITT	"	173/227	154/226	0.0562	– 0.30 , 16.42
	Per-Protocol	"	65/78	52/69	0.2907	– 5.44 , 21.70
	All randomized	ITT assignment	173/230	154/229	0.0612	– 0.42 , 16.37
	Modified ITT	"	173/227	154/226	0.0562	– 0.30 , 16.42
	Per-Protocol	"	65/78	52/69	0.2907	– 5.44 , 21.70
Microbiological cure	All randomized	Actual assignment	86/110	76/103	0.5220	– 7.23 , 16.17
	Modified ITT	"	86/109	76/101	0.6230	– 7.85 , 15.25
	Per-Protocol	"	64/78	58/69	0.8281	– 14.47 , 10.68
	All randomized	ITT assignment	86/110	76/103	0.5220	– 7.23 , 16.17
	Modified ITT	"	86/109	76/101	0.6230	– 7.85 , 15.25
	Per-Protocol	"	64/78	58/69	0.8281	– 14.47 , 10.68

***Confidence interval on microbiological cure is 95%**

2.3.6.2 Reviewer's conclusion of Study 3-02

The 95.2% CI for the clinical cure (– 5.44%, 21.70%) is in favor of gatifloxacin. Considering this confidence interval and delta equal to 6%, this reviewer concludes that the submitted data support non-inferiority of gatifloxacin compared to ofloxicin for clinical cure. However, this result needs to be interpreted in the context of assay sensitivity, which is addressed in the next section.

The 95% CI for the microbiological cure (-14.47%, 10.68%) is in favor of gatifloxacin. Considering this confidence interval and delta equal to 15%, this reviewer concludes that the submitted data also support non-inferiority of gatifloxacin compared to ofloxicin for microbiological cure.

2.4 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

2.4.1 OVER ALL EVALUATION

There were two studies in this submission. The first study (#3-01) was a placebo control study, while the second one (#3-02) was a non-inferiority study, without a placebo arm. In the absence of placebo arm in second study it was difficult to make an overall conclusion of effectiveness of gatifloxacin from the combined efficacy results of the two studies, especially when there was no convincing result from the first study.

The per-protocol population of placebo arm in Study #3-01 had a clinical cure rate of 0.58 (28/48) with 95% confidence interval 0.43 to 0.73 (21/48 to 35/48). A worst case scenario comparison of gatifloxacin in Study #3-02 with control of Study #3-01 can be done by comparing the gatifloxacin of Study #3-02 with upper 95% confidence limit of control of Study #3-01. The following table contains this reviewer's results of such comparisons.

Text Table 10: Comparison of Gatifloxacin of Study # 3-02 and Placebo of Study # 3-01 for clinical cure
(Reviewer's Table)

Comparison*	Gatiflox. (Study 3-02)	Placebo (Study 3-01)	P-Value	95% C.I. On difference (Gatiflox. - Placebo)
Gatifloxacin vs Observed values of Placebo (Observed case)	65/78	28/48	0.0032	0.0783 , 0.4137
Gatifloxacin vs Upper 95% confidence limit of Placebo (Worst case)	65/78	35/48	0.1792	– 0.0490 , 0.2668
Gatifloxacin vs Upper 75% confidence limit of Placebo	65/78	32/48	0.0328	0.0026 , 0.3300

*** For gatifloxacin vs Upper 85% or 80% confidence limit of placebo the lower 95% confidence limits were negative**

Text Table 10 shows that gatifloxacin group of Study # 3-02 was statistically significantly different from the observed placebo of Study # 3-01. Gatifloxacin group of Study # 3-02 was also statistically significantly different from the upper 75% confidence limit of placebo of Study #3-01. However, it was not statistically significantly different from the upper 80% (therefore, also from the upper 95%) confidence limit of placebo of Study # 3-01. From this results this reviewer could not conclude of a convincing superiority of gatifloxacin in Study # 3-02 over the placebo of Study # 3-01. This reviewer concluded, like Study # 3-301, the result was again borderline significant.

2.4.2 CONCLUSIONS AND RECOMMENDATIONS

Results of the first study (# 3-01) showed a borderline significant efficacy in favor of gatifloxacin for the primary clinical endpoint (clinical cure). In addition three centers (#121, #125, and #128) showed efficacy in favor of placebo. These three centers contributed about 40% of the total subjects in the trial. The second study (# 3-02) met the 6% delta criterion for 95.2% confidence interval on the difference in success rates of clinical cure, establishing non-inferiority of gatifloxacin to ofloxacin. However, this result was not convincing because of the assay sensitivity concerns. An evaluation of the assay sensitivity of the second study using the placebo of the first study gave only a borderline statistical significance.

Thus, considering the primary clinical endpoint, this reviewer concluded that overall there was a borderline statistically significant evidence of effectiveness of gatifloxacin in the treatment of bacterial conjunctivitis. The microbiological cure showed statistically significant evidence of effectiveness. A clinical consideration is necessary for making a final clinical decision.

M. Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: M. F. Huque, Ph.D.
Division Director, Biometrics III

cc:
Archival NDA 21-493
HFD-550/Division File
HFD-550/Dr. Chambers
HFD-550/Dr. Harris
HFD-550/Mr. Rodrigues

HFD-725/ Chron
HFD-725/ Dr. Huque
HFD-725/ Dr. Lin
HFD-725/ Dr. Rahman
HFD-700/Dr. Anello

3 APPENDIX

3.1 TABLE 1A: PATIENT'S DISPOSITION STUDY 3-01 (SAFETY POPULATION)

(Sponsor's Table: Section 14.1 Table 1 of Sponsor's Submission)

	0.3% GFLX (n=134)		Placebo (n=131)		Total (n=265)	
Total Number Completed	123	(91.8%)	124	(94.7%)	247	(93.2%)
Total Number Discontinued	11	(8.2%)	7	(5.3%)	18	(6.8%)
Reason for Early Withdrawal						
Adverse Event	3	(2.2%)	1	(0.8%)	4	(1.5%)
Protocol Violation	1	(0.7%)	0	(0.0%)	1	(0.4%)
Withdrew Consent	3	(2.2%)	1	(0.8%)	4	(1.5%)
Lost to Follow-Up	2	(1.5%)	1	(0.8%)	3	(1.1%)
Non-compliance	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Failure	2	(1.5%)	3	(2.3%)	5	(1.9%)
Did Not Meet Inclusion Criteria	0	(0.0%)	1	(0.8%)	1	(0.4%)
Pregnancy	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Unmasked	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other	0	(0.0%)	0	(0.0%)	0	(0.0%)

Source: Data Listing 16.2.1.

3.2 TABLE 1B: PATIENT'S DISPOSITION STUDY 3-01 (MITT POPULATION)

(Sponsor's Table: Section 14.4 Table 8 of Sponsor's Submission)

	0.3% GFLX (n=133)		Placebo (n=128)		Total (n=261)	
Total Number Completed	125	(94.0%)	122	(95.3%)	247	(94.6%)
Total Number Discontinued	8	(6.0%)	6	(4.7%)	14	(5.4%)
Reason for Early Withdrawal						
Adverse Event	3	(2.3%)	1	(0.8%)	4	(1.5%)
Protocol Violation	1	(0.8%)	0	(0.0%)	1	(0.4%)
Withdrew Consent	1	(0.8%)	1	(0.8%)	2	(0.8%)
Lost to Follow-Up	2	(1.5%)	0	(0.0%)	2	(0.8%)
Non-compliance	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Failure	1	(0.8%)	3	(2.3%)	4	(1.5%)
Did Not Meet Inclusion Criteria	0	(0.0%)	1	(0.8%)	1	(0.4%)
Pregnancy	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Unmasked	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other	0	(0.0%)	0	(0.0%)	0	(0.0%)

Source: Data Listing 16.2.1.

SENJU00:[PROGRAM.TABLE]DISPO.SAS / DSP4B, 21DEC2001, 15:57 SAS Version 6.12

Study: SPCL-GFLX 3/01

3.3 TABLE 2: COMPARISON OF PATIENT BASELINE CHARACTERISTICS STUDY 3-01

(Safety Population)

(Sponsor's Table: Section 14.1 Table 2 of Sponsor's Submission)

	0.3% GFLX (n=134)	Placebo (n=131)	Total (n=265)	P-value [a]
Age (years)				
N	134	131	265	0.178
Mean (SD)	40.4 (23.86)	36.5 (22.99)	38.4 (23.47)	
Median	39.0	37.0	38.0	
(Min, Max)	1, 90	1, 90	1, 90	
<=12	25 (18.7%)	25 (19.1%)	50 (18.9%)	
>12	109 (81.3%)	106 (80.9%)	215 (81.1%)	
Duration of Current Episode (days)				
N	134	131	265	0.887
Mean (SD)	1.7 (1.25)	1.6 (1.16)	1.7 (1.20)	
Median	2.0	2.0	2.0	
(Min, Max)	0, 8	0, 6	0, 8	

[a] P-value for age from F test from an ANOVA model containing term for treatment. P-value for duration of current episode from Wilcoxon rank sum test. P-values for sex, race, iris color (dark:brown, light:blue,green,other), infection, number of organisms, and reference eye from Fisher exact test.
[b] Reference eye is the eye included in efficacy analysis.

Table 2 (Continued)

Table 2: Comparison of Patient Baseline Characteristics Study 3-01

		0.3% GFLX (n=134)		Placebo (n=131)		Total (n=265)		P-value [a]
Sex								
	Male	47	(35.1%)	45	(34.4%)	92	(34.7%)	1.000
	Female	87	(64.9%)	86	(65.6%)	173	(65.3%)	
Race								
	Caucasian 106		(79.1%)	108	(82.4%)	214	(80.8%)	0.643
	African American	16	(11.9%)	13	(9.9%)	29	(10.9%)	
	Asian/Pacific Islander	1	(0.7%)	0	(0.0%)	1	(0.4%)	
	Hispanic	9	(6.7%)	10	(7.6%)	19	(7.2%)	
	Native American/Alaskan	0	(0.0%)	0	(0.0%)	0	(0.0%)	
	Other	2	(1.5%)	0	(0.0%)	2	(0.8%)	
	Caucasian 106		(79.1%)	108	(82.4%)	214	(80.8%)	0.535
	non-Caucasian	28	(20.9%)	23	(17.6%)	51	(19.2%)	
Iris Color								
	Brown	72	(53.7%)	62	(47.3%)	134	(50.6%)	0.454
	Blue	31	(23.1%)	42	(32.1%)	73	(27.5%)	
	Green	22	(16.4%)	19	(14.5%)	41	(15.5%)	
	Other	9	(6.7%)	8	(6.1%)	17	(6.4%)	
	Dark	72	(53.7%)	62	(47.3%)	134	(50.6%)	0.327
	Light	62	(46.3%)	69	(52.7%)	131	(49.4%)	
Infection								
	Unilateral	88	(65.7%)	87	(66.4%)	175	(66.0%)	1.000
	Bilateral	46	(34.3%)	44	(33.6%)	90	(34.0%)	
Number of Organisms Above Pathological Threshold in Reference Eye								
	0	62	(46.3%)	69	(52.7%)	131	(49.4%)	0.140
	1	57	(42.5%)	40	(30.5%)	97	(36.6%)	
	2	8	(6.0%)	15	(11.5%)	23	(8.7%)	
	3 or more	7	(5.2%)	7	(5.3%)	14	(5.3%)	
Reference Eye [b]								
	Left	54	(40.3%)	56	(42.7%)	110	(41.5%)	0.710
	Right	80	(59.7%)	75	(57.3%)	155	(58.5%)	

3.4 TABLE 3A: PATIENT'S DISPOSITION STUDY 3-02 (SAFETY POPULATION)

(Sponsor's Table: Section 14.1 Table 1 of Sponsor's Submission)

	0.3% GFLX (n=230)		0.3% OFLX (n=229)		Total (n=459)	
Total Number Completed	220	(95.7%)	215	(93.9%)	435	(94.8%)
Total Number Discontinued	10	(4.3%)	14	(6.1%)	24	(5.2%)
Reason for Early Withdrawal						
Adverse Event	3	(1.3%)	6	(2.6%)	9	(2.0%)
Protocol Violation	1	(0.4%)	0	(0.0%)	1	(0.2%)
Withdrew Consent	0	(0.0%)	0	(0.0%)	0	(0.0%)
Lost to Follow-Up	5	(2.2%)	6	(2.6%)	11	(2.4%)
Non-compliance	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Failure	0	(0.0%)	0	(0.0%)	0	(0.0%)
Did Not Meet Inclusion Criteria	1	(0.4%)	0	(0.0%)	1	(0.2%)
Pregnancy	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Unmasked	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other	0	(0.0%)	2	(0.9%)	2	(0.4%)

Source: Data Listing 16.2.1.

3.5 TABLE 3B: PATIENT'S DISPOSITION STUDY 3-02 (MITT POPULATION)

(Sponsor's Table: Section 14.4 Table 8 of Sponsor's Submission)

	0.3% GFLX (n=220)		0.3% OFLX (n=222)		Total (n=442)	
Total Number Completed	214	(97.3%)	211	(95.0%)	425	(96.2%)
Total Number Discontinued	6	(2.7%)	11	(5.0%)	17	(3.8%)
Reason for Early Withdrawal						
Adverse Event	3	(1.4%)	5	(2.3%)	8	(1.8%)
Protocol Violation	1	(0.5%)	0	(0.0%)	1	(0.2%)
Withdrew Consent	0	(0.0%)	0	(0.0%)	0	(0.0%)
Lost to Follow-Up	2	(0.9%)	4	(1.8%)	6	(1.4%)
Non-compliance	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Failure	0	(0.0%)	0	(0.0%)	0	(0.0%)
Did Not Meet Inclusion Criteria	0	(0.0%)	0	(0.0%)	0	(0.0%)
Pregnancy	0	(0.0%)	0	(0.0%)	0	(0.0%)
Treatment Unmasked	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other	0	(0.0%)	2	(0.9%)	2	(0.5%)

Note: The intended randomized treatment is unknown for 11 patients; they were excluded from the analysis.

Source: Data Listing 16.2.1.

3.6 TABLE 4: COMPARISON OF PATIENT BASELINE CHARACTERISTICS STUDY 3-02

(Safety Population)

(Sponsor's Table: Section 14.1 Table 2 of Sponsor's Submission)

	0.3% GFLX (n=230)	0.3% OFLX (n=229)	Total (n=459)	P-value [a]
Age (years)				
N	230	229	459	0.710
Mean (SD)	38.9 (23.80)	39.7 (25.39)	39.3 (24.58)	
Median	37.0	36.0	36.0	
(Min, Max)	1, 95	1, 99	1, 99	
<=12	36 (15.7%)	38 (16.6%)	74 (16.1%)	
>12	194 (84.3%)	191 (83.4%)	385 (83.9%)	
Duration of Current Episode (days)				
N	230	229	459	0.167
Mean (SD)	1.5 (1.01)	1.6 (1.09)	1.5 (1.05)	
Median	1.0	2.0	1.0	
(Min, Max)	0, 4	0, 4	0, 4	

[a] P-value for age from F test from an ANOVA model containing term for treatment. P-value for duration of current episode from Wilcoxon rank sum test. P-values for sex, race, iris color (dark:brown, light:blue,green,other), infection, number of organisms, and reference eye from Fisher exact test.
[b] Reference eye is the eye included in efficacy analysis.

Table 4 (Continued)

	0.3% GFLX (n=230)		0.3% OFLX (n=229)		Total (n=459)		P-value [a]
Sex							
Male	92	(40.0%)	78	(34.1%)	170	(37.0%)	0.209
Female	138	(60.0%)	151	(65.9%)	289	(63.0%)	
Race							
Caucasian	167	(72.6%)	153	(66.8%)	320	(69.7%)	0.328
African American	26	(11.3%)	23	(10.0%)	49	(10.7%)	
Asian/Pacific Islander	2	(0.9%)	2	(0.9%)	4	(0.9%)	
Hispanic	32	(13.9%)	47	(20.5%)	79	(17.2%)	
Native American/Alaskan	0	(0.0%)	2	(0.9%)	2	(0.4%)	
Other	3	(1.3%)	2	(0.9%)	5	(1.1%)	
Caucasian	167	(72.6%)	153	(66.8%)	320	(69.7%)	0.188
non-Caucasian	63	(27.4%)	76	(33.2%)	139	(30.3%)	
Iris Color							
Brown	119	(51.7%)	118	(51.5%)	237	(51.6%)	0.648
Blue	69	(30.0%)	70	(30.6%)	139	(30.3%)	
Green	24	(10.4%)	29	(12.7%)	53	(11.5%)	
Other	18	(7.8%)	12	(5.2%)	30	(6.5%)	
Dark	119	(51.7%)	118	(51.5%)	237	(51.6%)	1.000
Light	111	(48.3%)	111	(48.5%)	222	(48.4%)	
Infection							
Unilateral	145	(63.0%)	149	(65.1%)	294	(64.1%)	0.697
Bilateral	85	(37.0%)	80	(34.9%)	165	(35.9%)	
Number of Organisms Above Pathological Threshold in Reference Eye							
0	121	(52.6%)	126	(55.0%)	247	(53.8%)	0.227
1	88	(38.3%)	74	(32.3%)	162	(35.3%)	
2	13	(5.7%)	23	(10.0%)	36	(7.8%)	
3 or more	8	(3.5%)	6	(2.6%)	14	(3.1%)	
Reference Eye [b]							
Left	93	(40.4%)	95	(41.5%)	188	(41.0%)	0.850
Right	137	(59.6%)	134	(58.5%)	271	(59.0%)	

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/s/

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