U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22548
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this submission, the Applicant seeks approval of gatifloxacin 0.5% ophthalmic solution BID for the treatment of acute bacterial conjunctivitis. The Applicant submitted two pivotal studies: study 198782-004, and study 198782-005. Both studies 198782-004 and 198782-005 were randomized, double masked, multi-center, and vehicle-controlled superiority trials.

In study 198782-004, for the primary analysis (including all data collected for Day 6 Visit regardless whether the actual visit occurred on day 6 or later), the clinical success rate was 74.9% (125/167) for gatifloxacin 0.5% ophthalmic solution and 65.2% (103/158) for Vehicle in the study eye. The treatment difference was 9.7% with 95% confidence interval of (-0.3%, 19.6%). This efficacy result was statistically marginal with p-value slightly above the 0.05 significance level (p-value = 0.057).

In study 198782-005, for the primary analysis (using only data collected up to and including day 6), the clinical success rate was 51.8% (86/166) for gatifloxacin 0.5% ophthalmic solution and 41.3% (69/167) for Vehicle in the study eye. The treatment difference was 10.5% with 95% confidence interval of (-0.2%, 21.2%). This efficacy result was also statistically marginal with p-value slightly above the 0.05 significance level (p-value = 0.055).

1.2 Brief Overview of Clinical Studies

Studies 198782-004 and 198782-005 were identically designed efficacy/safety studies. They were multi-center, double-blinded, randomized, Vehicle-controlled studies to evaluate the safety and efficacy of gatifloxacin ophthalmic solution 0.5% in the treatment of acute bacterial conjunctivitis. The test drugs (gatifloxacin and vehicle) were administered every 2 hours for up to eight times on the first day and twice daily (BID) for days 2 to 5. The studies consisted of three scheduled office visits: day 1 (baseline), day 4 (±1), and day 6 (+1).

For both studies, the primary efficacy endpoint was clinical success at Day 6 Visit, defined as clearing (i.e., score = 0) of both conjunctival hyperemia and conjunctival discharge in the study eye. For study 198782-004, the primary efficacy analysis was done including all data collected for Day 6 Visit regardless whether the actual visit occurred on day 6 or later (referred as "Day 6 Visit Analysis" throughout this review). After unblinding Study 198782-004 that showed more favorable result with the Up to Day 6 analysis (using all data collected up to and including day 6) compared with the Day 6 Visit analysis, the Applicant revised the primary efficacy analysis for Study 198782-005; the primary efficacy analysis for this study was changed to the Up to Day 6 analysis instead of the Day 6 Visit analysis.

Study 198782-004 enrolled a total of 578 patients from 51 study sites in the U.S: 287 randomized to receive gatifloxacin, of whom 167 were culture positive, and 291 randomized to receive vehicle, of which 158 were culture positive.

Study 198782-005 enrolled a total of 859 patients from 29 study sites in India and 10 sites in U.S: 430 of them were randomized to receive gatifloxacin, of whom 179 were culture positive, and 429 were randomized to receive vehicle, of which 185 were culture positive. The Applicant had serious concerns about data integrity at one Indian site (site 13020). Of 72 patients randomized at that site, no one discontinued due to adverse events or was lost to follow-up. Therefore site 13020 was excluded from the primary analyses by the Applicant. The efficacy results including data from site 13020 were also analyzed by the Applicant as sensitivity analyses.

1.3 Statistical Issues and Findings

There are no major statistical issues for both studies. However, the primary efficacy results for both studies were statistically marginal with p-values slightly above the 0.05 significance level: p-value = 0.057 for study 198782-004, and p-value = 0.055 for study 198782-005.

To further examine the robustness of the efficacy results, the statistical reviewer performed additional sensitivity analyses using different study durations (from Day 4 Visit to the day that last patient came in for Day 6 Visit evaluation); the results are presented in the following table, where the shaded rows are the primary efficacy results. Although the clinical success rates for either gatifloxacin or vehicle were almost 15% higher in study 198782-004 compared to study 198782-005, the point estimates of the treatment difference were relatively consistent and around 10% in both studies.

It should be noted that both studies were powered based on the assumption of 16% treatment difference between gatifloxacin and vehicle groups in the clinical success rate. However, the observed clinical success rate was only around 10%. Thus both studies were underpowered.

It should also be noted that study 198782-005 would have demonstrated statistically significant results of the primary efficacy endpoint if the Applicant had followed the original analysis plan and not changed the analysis from Day 6 Visit analysis to Up to Day 6 analysis.

Table 1: Statistical Reviewer's Sensitivity Analysis of Clinical Success

Study 198782-004				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	56/167 (33.5%)	33/158 (20.9%)	0.010	12.6% (3.1%, 22.2%)
Day 6 Visit				
Up to Day 6	107/167 (64.1%)	79/158 (50.0%)	0.010	14.1% (3.4%, 24.7%)
Up to Day 7	119/167 (71.3%)	97/158(61.4%)	0.060	9.9% (-0.3%, 20.1%)
Up to Day 8	123/167 (73.7%)	101/158 (63.9%)	0.058	9.7% (-0.3%, 19.8%)
Up to Day 9	125/167 (74.9%)	102/158 (64.6%)	0.044	10.3% (0.4%, 20.2%)
Up to Day 14	125/167 (74.9%)	103/158 (65.2%)	0.057	9.7% (-0.3%, 19.6%)
Day 6 Visit	125/167 (74.9%)	103/158 (65.2%)	0.057	9.7% (-0.3%, 19.6%)
Study 198782-005				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	23/166 (13.9%)	17/167 (10.2%)	0.30	3.7% (-3.3%, 10.7%)
Day 6 Visit				
Up to Day 6	86/166 (51.8%)	69/167 (41.3%)	0.055	10.5% (-0.2%, 21.2%)
Up to Day 7	99/166 (59.6%)	76/167 (45.5%)	0.010	14.1% (3.5%, 24.8%)
Up to Day 8	99/166 (59.6%)	77/167 (46.1%)	0.014	13.5% (2.9%, 24.2%)
Up to Day 9	99/166 (59.6%)	78/167 (46.7%)	0.018	12.9% (2.3%, 23.6%)
Day 6 Visit	99/166 (59.6%)	78/167 (46.7%)	0.018	12.9% (2.3%, 23.6%)

2. INTRODUCTION

2.1 Overview

Gatifloxacin is a fourth-generation 8-methoxy fluroquinolone that exerts its antibacterial action by inhibiting DNA gyrase (an enzyme involved in the replication, transcription and repair of bacterial DNA) and topoisomerase IV (an enzyme that plays a key role in the partitioning of the chromosomal DNA during bacterial cell division). Gatifloxacin has been shown to be active, both in vitro and in conjunctival infections, against most strains of *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Haemophilus influenzae, Corynebacterium propinquum,* and *Streptococcus mitis.* Gatifloxacin 0.3% ophthalmic solution (ZYMAR®) was approved in the US in March 2003 (NDA21493) for the indication of bacterial conjunctivitis in adults and pediatric patients age 1 year or older. The dosing regimen in the clinical trials of the approved NDA was up to 8 times daily for the first 2 days, and 4 times daily for the subsequent 3 days.

The Sponsor reformulated a higher concentration of gatifloxacin, 0.5% and decreased the dosing frequency after the first day to twice daily for the new concentration. The following table shows the difference of daily drug exposure given bilaterally between the approved 0.3% formulation and 0.5% formulation in clinical trials.

Table 2: Drug Exposure

	0.5% formulation	0.3% formulation
Day 1	0.08	0.048
Day 2	0.02	0.048
Day 3	0.02	0.024
Day 4	0.02	0.024
Day 5	0.02	0.024
Total	0.14	0.168

Given bilaterally for five days with decreased dosing frequency after the first day, the total drug exposure of the 0.5% formulation in five days is 16.7% less than that of the 0.3% formulation, which could result in fewer adverse events. Therefore, the Sponsor conducted two pivotal studies 198782-004, and 198782-005 to evaluate the safety and efficacy of the new formulation with the new dosing regimen. Both study 198782-004 and study 198782-005 were 6-day, multi-center, double-blinded, randomized, vehicle-controlled, parallel-group studies comparing gatifloxacin ophthalmic solution 0.5% with that of gatifloxacin vehicle for the treatment of acute bacterial conjunctivitis in patients > 1 year of age.

2.2 Data Sources

The Sponsor's study reports and datasets for studies 198782-004, and 198782-005 are available on the EDR at \\CDSESUB1\EVSPROD\NDA022548.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Designs and Endpoints

Both study 198782-004 and 198782-005 were identically designed phase 3 studies. They were multi-center, randomized, double-masked, parallel-group, and vehicle-controlled studies. The primary objective of both studies was to evaluate the safety and efficacy of gatifloxacin ophthalmic solution 0.5% in the treatment of acute bacterial conjunctivitis.

In both studies, subjects who met the criteria for enrollment were randomly assigned to use either gatifloxacin 0.5%, or its vehicle in a 1:1 ratio. The duration of treatments was 5 days. On treatment day 1, patients instilled 1 drop of study medication in each qualified eye every 2 hours up to 8 times total. On days 2 to 5, patients in both treatment groups were instructed to put one drop of the assigned study medication in each qualified eye twice daily. The studies consisted of three scheduled office visits: day 1 (baseline), day 4, and day 6. The Day 6 Visit was to occur between 12 hours (minimum) to 48 hours (maximum) after the last dose of study medication.

In both studies, a patient was considered as having bacterial conjunctivitis with a minimum of a 2+ (moderate) conjunctival hyperemia and a 1+ (mild) discharge in at least one eye to be treated with study medication. Both signs for each eye were measured on a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe).

Subjects may have one eye or both eyes with clinical diagnose of acute bacterial conjunctivitis at Day 1 and qualified to be treated. Such eye(s) was (were) referred to as "qualified eye(s)". However, only **one** eye of each subject would be used for efficacy analyses. If both eyes qualified for treatment, the eye with positive bacterial conjunctivitis culture at day 1 was designated as the study eye. If both qualified eyes were culture positive or both qualified eyes were culture negative at day 1, then the right eye was the study eye. If only one eye qualified, this eye was the study eye.

The primary efficacy endpoints for both studies were clinical success at day 6 time point. Clinical success was defined as clearing (i.e., score=0) of both conjunctival hyperemia and conjunctival discharge in the study eye. The difference between the two studies was how the primary efficacy end point was analyzed. In the original protocols, both studies had the same primary efficacy endpoint: clinical success rate at Day 6 Visit, including data collected on and after day 6. For study 198782-004, the primary efficacy endpoint was analyzed as planned. After unblinding Study 198782-004 that showed more favorable result with the Up to Day 6 analysis (using all data collected up to and including day 6) compared with the Day 6 Visit analysis, the Applicant revised the primary efficacy analysis for Study 198782-005; the primary efficacy analysis for this study was changed to the Up to Day 6 analysis instead of the Day 6 Visit analysis.

There were four analysis populations for both studies: Intent-to-Treat (ITT) population, modified Intent-to-Treat (mITT) population, Per Protocol (PP) population, and safety population. The ITT

population consisted of all randomized subjects. The mITT population consisted of all ITT subjects who were culture positive at baseline. The mITT population was the primary efficacy analysis population. For all planned efficacy analyses based on mITT population, patients were included in the treatment group to which they were randomized. The Per Protocol (PP) population consisted of all mITT subjects with at least one follow-up visit, who were treated with drug to which they were randomized and had no major protocol deviations.

The safety population consisted of randomized and treated patients. For safety analyses, patients were included in the treatment group to which they were actually treated.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Study 198782-004

A total of 578 patients were enrolled and 552 patients (95.5%) completed the study. Disposition of all enrolled patients is shown in Table 3.

Table 3: Study 198782-004 Disposition of All Enrolled Subjects

	Gatifloxacin	Vehicle	Total
All enrolled patients	287	291	578
Completed	276 (96.2%)	276 (94.8%)	552 (95.5%)
Discontinued	11 (3.8%)	15 (5.2%)	26 (4.5%)
Adverse events	2 (0.7%)	5 (1.7%)	7 (1.2%)
Ocular	2 (0.7%)	5 (1.7%)	7 (1.2%)
Non-ocular	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of efficacy	2 (0.7%)	2 (0.7%)	4 (0.7%)
Lost to follow-up	3 (1.0%)	0 (0.0%)	3 (0.5%)
Personal reasons	0 (0.0%)	3 (1.0%)	3 (0.5%)
Protocol violation	1 (0.3%)	0 (0.0%)	1 (0.2%)
Other	3 (1.0%)	5 (1.7%)	8 (1.4%)

Source: Sponsor's study 198782-004 report Table 10-1

There were three patients who did not receive the treatment to which they were randomized: one patient (10009-1632) randomized to gatifloxacin who received vehicle, and two patients (10034-1319 and 10075-1338) randomized to vehicle who received gatifloxacin. For all planned efficacy analyses based on mITT population, these three patients were included in the group to which they were randomized.

Summary of the analysis populations is presented in the following table. The ITT population had 287 patients randomized to gatifloxacin, 291 to vehicle. Of the 578 patients in the ITT population, 325 patients were included in the mITT population, thus the culture positive rate in this study was 56.2% (167/287 (58.2%) in the gatifloxacin group and 158/291 (54.3%) in the vehicle group). In the mITT population, there were 25 patients in the gatifloxacin group and 20 patients in the vehicle group with important protocol deviations who were therefore excluded

from the PP analysis. The safety population included 288 patients in gatifloxacin group, 289 in vehicle group.

Table 4: Study 198782-004 Analysis Population by Treatment Arm

Population	Gatifloxacin (% of ITT)	Vehicle (% of ITT)
ITT	287 (100%)	291 (100%)
mITT	167 (58.2%)	158 (54.3%)
PP	142 (49.5%)	138 (47.4%)
Safety	288	289

Source: Sponsor's study 198782-004 report Table 10-2

The summaries of baseline demographic characteristics are presented in Table 5. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 5: Study 198782-004 Demographic Characteristics

ITT Population							
		Gatifloxacin (N=287)		**Vehicle (N=291)**		**Total (N=269)**	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	126	(43.9%)	119	(40.9%)		
	Female	161	(56.1%)	172	(59.1%)		
Age	**MEAN**		30.7		30.6		30.7
	SD		25.38		24.36		24.85
	MEDIAN		24.0		25.0		24.0
	RANGE		1 to 89		1 to 92		1 to 92
Race	**Caucasian**	150	(52.3%)	156	(53.6%)	306	(52.9%)
	Black or African American	29	(10.1%)	23	(7.9%)	52	(9.0%)
	Asian	5	(1.7%)	13	(4.5%)	18	(3.1%)
	Hispanic	101	(35.2%)	91	(31.3%)	192	(33.2%)
	Other	2	(0.7%)	8	(2.7%)	10	(1.7%)
mITT Population							
		Gatifloxacin (N=167)		**Vehicle (N=158)**		**Total (N=325)**	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	83	(49.7%)	74	(46.8%)	157	(48.3%)
	Female	84	(50.3%)	84	(53.2%)	168	(51.7%)
Age	**MEAN**		30.7		26.4		28.6
	SD		28.68		24.52		26.78
	MEDIAN		19.0		16.0		18.0
	RANGE		1 to 89		1 to 88		1 to 89
Race	**Caucasian**	84	(50.3%)	84	(53.2%)	168	(51.7%)
	Black or African American	12	(7.2%)	10	(6.3%)	22	(6.8%)
	Asian	3	(1.8%)	7	(4.4%)	10	(3.1%)
	Hispanic	66	(39.5%)	51	(32.3%)	117	(36.0%)
	Other	2	(1.2%)	6	(3.8%)	8	(2.5%)

Source: Sponsor's study 198782-004 report Tables 14.1-2.1 and 14.1-2.2

Study 198782-005

A total of 859 patients were enrolled, 770 in India and 89 in the US. Of these 859 patients, 800 (93.1%) completed the study. Completion rates were similar in the treatment groups: 402/430 (93.5%) in the gatifloxacin group and 398/429 (92.8%) in the vehicle group. The most frequent reason for discontinuation in both groups was loss to follow up. The following table shows disposition of all enrolled patients.

Table 6: Study 198782-005 Disposition of all enrolled subjects

	Gatifloxacin	Vehicle	Total
All enrolled patients	430	429	859
Completed	402 (93.5%)	398 (92.8%)	800 (93.1%)
Discontinued	28 (6.5%)	31 (7.2%)	59 (6.9%)
Adverse events	6 (1.4%)	4 (0.9%)	10 (1.2%)
Ocular	4 (0.9%)	3 (0.7%)	7 (0.8%)
Non-ocular	2 (0.5%)	1 (0.2%)	3 (0.3%)
Lack of efficacy	0 (0%)	0 (0%)	0 (0%)
Lost to follow-up	18 (4.2%)	20 (4.7%)	38 (4.4%)
Personal reasons	2 (0.5%)	2 (0.5%)	4 (0.5%)
Protocol violation	1 (0.2%)	1 (0.2%)	2 (0.2%)
Other	1 (0.2%)	4 (0.9%)	5 (0.6%)

Source: Sponsor's study 198782-005 report Table 10-1

Summary of analysis population is presented in the following table. The Intent to Treat (ITT) study population included all 859 randomized subjects. The mITT population consisted of the 364 patients with positive cultures at baseline: 179 in the gatifloxacin group and 185 in the vehicle group. The PP population consisted of 173 patients in the gatifloxacin group and 174 in the vehicle group.

The Applicant had serious concerns about data integrity at one Indian site (site 13020). Of 72 patients randomized at that site, no one discontinued due to adverse events or was lost to follow-up. Therefore site 13020 was excluded from the primary analyses by the Applicant. The ITT completion rate (92.6%) when the 72 patients (36 in each treatment group) from that site were excluded was similar to that of the entire ITT population (93.1%).

Table 7: Study 198782-005 Analysis Population by Treatment Arm

	All Sites		Site 13020 Excluded	
Population	Gatifloxacin	Vehicle	Gatifloxacin	Vehicle
ITT	430 (100%)	429 (100%)	394 (100%)	393 (100%)
mITT	179 (41.5%)	185 (43.1%)	166 (42.1%)	167 (42.5%)
PP	173 (40.2%)	174 (40.6%)	160 (40.6%)	156 (39.7%)
Safety	429	427	Not applicable	Not applicable

Source: Sponsor's study 198782-004 report Table 10-2

When all randomized patients at all sites were included, there were 859 patients in the ITT population, ranging in age from 1 to 87 years. The summaries of baseline demographic

characteristics are presented in Table 8. There was no marked difference in the baseline characteristics between the two treatment groups. The majority of the patients in both groups were non-Caucasian (96.0% and 97.0% in the gatifloxacin and vehicle groups, respectively), primarily Asian because majority of the study sites were in India.

Table 8: Study 198782-005 Demographic Characteristics

ITT Population							
		Gatifloxacin (N=430)		**Vehicle (N=429)**		**Total (N=859)**	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	247	(57.4%)	273	(63.6%)		
	Female	183	(42.6%)	156	(36.4%)		
Age	**MEAN**		38.5		36.6		37.5
	SD		19.81		19.72		19.78
	MEDIAN		36.0		35.0		35.0
	RANGE		1 to 86		1 to 87		1 to 87
Race	**Caucasian**	17	(4.0%)	13	(3.0%)	30	(3.5%)
	Black or African American	4	(0.9%)	6	(1.4%)	10	(1.2%)
	Asian	387	(90.0%)	388	(90.4%)	775	(90.2%)
	Hispanic	22	(5.1%)	22	(5.1%)	44	(5.1%)
	Other	0	(0.0%)	0	(0.0%)	0	(0.0%)
mITT Population							
		Gatifloxacin (N=179)		**Vehicle (N=185)**		**Total (N=364)**	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	98	(49.7%)	115	(46.8%)	157	(48.3%)
	Female	81	(50.3%)	70	(53.2%)	168	(51.7%)
Age	**MEAN**		39.3		38.2		38.8
	SD		20.11		20.37		20.22
	MEDIAN		37		36.0		36.0
	RANGE		1 to 86		1 to 87		1 to 87
Race	**Caucasian**	3	(1.7%)	3	(1.6%)	6	(1.6%)
	Black or African American	1	(0.6%)	3	(1.6%)	4	(1.1%)
	Asian	166	(92.7%)	169	(91.4%)	335	(92.0%)
	Hispanic	9	(5.0%)	10	(5.4%)	19	(5.2%)

Source: Sponsor's study 198782-004 report Tables 14.1-2.1 and 14.1-2.2

The following table summarized the demographic characteristics of the ITT and mITT analysis populations excluding subjects from site 13020.

Table 9: Study 198782-005 Demographic Characteristics Excluding Site 13020

ITT Population							
		Gatifloxacin (N=394)		Vehicle (N=393)		Total (N=787)	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	247	(57.4%)	273	(63.6%)	467	(59.3%)
	Female	183	(42.6%)	156	(36.4%)	320	(40.7%)
Age	**MEAN**		38.8		36.7		37.7
	SD		19.92		19.67		19.81
	MEDIAN		36		35.0		36.0
	RANGE		1 to 86		1 to 87		1 to 87
Race	**Caucasian**	17	(4.3%)	13	(3.3%)	30	(3.5%)
	Black or African American	4	(1.0%)	6	(1.5%)	10	(1.2%)
	Asian	351	(89.1%)	352	(89.6%)	775	(90.2%)
	Hispanic	22	(5.6%)	22	(5.6%)	44	(5.1%)
	Other	0	(0.0%)	0	(0.0%)	0	(0.0%)
mITT Population							
		Gatifloxacin (N=166)		Vehicle (N=167)		Total (N=364)	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	88	(53.0%)	100	(59.9%)	188	(56.5%)
	Female	78	(47.0%)	67	(40.1%)	145	(43.5%)
Age	**MEAN**		38.9		38.8		38.8
	SD		20.39		20.39		20.36
	MEDIAN		37.0		36.0		36.0
	RANGE		1 to 86		1 to 87		1 to 87
Race	**Caucasian**	3	(1.7%)	3	(1.6%)	6	(1.6%)
	Black or African American	1	(0.6%)	3	(1.6%)	4	(1.1%)
	Asian	166	(92.7%)	169	(91.4%)	335	(92.0%)
	Hispanic	9	(5.0%)	10	(5.4%)	19	(5.2%)

Source: Sponsor's study 198782-004 report Tables 14.1-2.5 and 14.1-2.6

The demographic characteristics excluding patients from site 13020 were consistent with those of all randomized patients at all sites.

3.1.3 Statistical Methodologies

Studies 198782-004 and 198782-005 were two identically designed pivotal studies. The studies were different in how the primary efficacy endpoint was defined. The statistical methodologies were the same for both studies except the primary endpoints analyses.

Primary Efficacy Endpoint

The primary efficacy variable was clinical success, defined as scores of 0 for both conjunctival hyperemia and mucopurulent discharge.

Efficacy Analysis Populations

There were four analysis populations: Intent-to-Treat (ITT) population, modified Intent-to-Treat (mITT) population, Per Protocol (PP) population, and safety population. The ITT population consisted of all randomized subjects. The mITT population consisted of all ITT subjects who were culture positive at baseline. The mITT population was the primary efficacy analysis population. For all planned efficacy analyses based on mITT population, patients were included in the treatment group to which they were randomized. The Per Protocol (PP) population consisted of all mITT subjects with at least one follow-up visit, who were treated with drug to which they were randomized and had no major protocol deviations.

The safety population consisted of randomized and treated patients. For safety analyses, patients were included in the treatment group to which they were actually treated.

Analysis of Primary Efficacy Endpoints

For study 198782-004, the primary efficacy endpoint was analyzed using the study eye including all data collected for the day 6 visit, regardless whether the actual visit occurred on day 6 or later (defined as the "Day 6 Visit analysis").

In Study 198782-005, the primary efficacy end point was analyzed using only data collected up to and including day 6 (defined as the "Up to Day 6 analysis").

The statistical null hypothesis was that there was no difference between Gatifloxacin 0.5% and vehicle in clinical success rates. The alternative hypothesis was that there existed a difference. All statistical hypotheses were 2-sided. A p-value ≤ 0.05 were considered statistically significant.

The clinical success rates were compared between the Gatifloxacin 0.5% and vehicle treatment groups using the Pearson's chi-square test. The last observation carried forward (LOCF) method was applied to impute missing values.

Determination of Sample Size

The sample size and power calculation were based on the assumption of a 57% clinical success rate for vehicle and a 16% treatment difference, estimated from the cure rate of a previous superiority study. With a sample size of 140 patients per treatment group in the mITT population, the power would be 80% to detect the 16% treatment difference using a 2-sided Pearson's chi-square at the 5% significance level.

It was expected that the culture positive rate in this study would be higher than previously reported (approximately 50%) with the use of a screening device (adenovirus antigen detector kits). Assuming a 60% culture positive rate, 467 randomized patients were expected to achieve 280 patients (140 per treatment group assuming an equal distribution of positive cultures in each treatment group) for the mITT population for the primary efficacy analysis.

3.1.4 Results and Conclusions

The following table presents the primary efficacy outcome for both studies. For study 198782-004, the primary analysis for efficacy was the Day 6 Visit analysis, which included all data collected for the day 6 visit, even if it was collected after day 6. The Up to Day 6 analysis is the primary efficacy analysis for study 198782-005, this analysis includes all data collected up to and including day 6, but excluding any day-6 visit data that was collected after the day 6 time point.

Table 10: Primary Efficacy Analysis Results

	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
Study 198782-004 Clinical Success (Day 6 Visit Analysis)	125/167 (74.9%)	103/158 (65.2%)	0.057	9.7% (-0.3%, 19.6%)
Study 198782-005 Clinical Success (Up to Day 6 Analysis)	86/166 (51.8%)	69/167 (41.3%)	0.055	10.5% (-0.2%, 21.2%)

Source: Sponsor's study 198782-004 report Table 11-1 and study 198782-005 report Table 11-1

Statistical Reviewer's Comments:
For both studies, the primary efficacy results are statistically marginal and the p-values were slightly above the 0.05 significance level.

Up to day 6 analyses were conducted by the Applicant as sensitivity analyses for study 198782-004 and for study 198782-005, vice versa. The following table shows the results of these sensitivity analyses.

Table 11: Sensitivity Analysis Results

	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
Study 198782-004 Clinical Success (Up to Day 6 Analysis)	107/167 (64.1%)	79/158 (50.0%)	0.010	14.1% (3.4%, 24.7%)
Study 198782-005 Clinical Success (Day 6 Visit Analysis)	99/166 (59.6%)	78/167 (46.7%)	0.018	12.9% (2.3%, 23.6%)

Source: Sponsor's study 198782-004 report Table 11-1 and study 198782-005 report Table 11-1

The sensitivity analysis results had lower p-values (p-value = 0.010 for Study 004, and p-value = 0.018 for Study 005) compared with the primary analyses. In order to examine the robustness of the efficacy results, the statistical reviewer performed additional sensitivity analyses using

different study durations (from study day 5 to the day that last patient came in for end-of-therapy evaluation); the results for both studies are listed in the following tables, where the shaded rows are the primary efficacy results.

Table 12: Statistical Reviewer's Sensitivity Analysis of Clinical Success

Study 198782-004				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	56/167 (33.5%)	33/158 (20.9%)	0.010	12.6% (3.1%, 22.2%)
Day 6 Visit				
Up to Day 6	107/167 (64.1%)	79/158 (50.0%)	0.010	14.1% (3.4%, 24.7%)
Up to Day 7	119/167 (71.3%)	97/158(61.4%)	0.060	9.9% (-0.3%, 20.1%)
Up to Day 8	123/167 (73.7%)	101/158 (63.9%)	0.058	9.7% (-0.3%, 19.8%)
Up to Day 9	125/167 (74.9%)	102/158 (64.6%)	0.044	10.3% (0.4%, 20.2%)
Up to Day 14	125/167 (74.9%)	103/158 (65.2%)	0.057	9.7% (-0.3%, 19.6%)
Day 6 Visit	125/167 (74.9%)	103/158 (65.2%)	0.057	9.7% (-0.3%, 19.6%)
Study 198782-005				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value[1]**	**Difference (95% CI)**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	23/166 (13.9%)	17/167 (10.2%)	0.30	3.7% (-3.3%, 10.7%)
Day 6 Visit				
Up to Day 6	86/166 (51.8%)	69/167 (41.3%)	0.055	10.5% (-0.2%, 21.2%)
Up to Day 7	99/166 (59.6%)	76/167 (45.5%)	0.010	14.1% (3.5%, 24.8%)
Up to Day 8	99/166 (59.6%)	77/167 (46.1%)	0.014	13.5% (2.9%, 24.2%)
Up to Day 9	99/166 (59.6%)	78/167 (46.7%)	0.018	12.9% (2.3%, 23.6%)
Day 6 Visit	99/166 (59.6%)	78/167 (46.7%)	0.018	12.9% (2.3%, 23.6%)

Within each study, the sensitivity analyses yield consistent point estimates for treatment difference in clinical success using different study duration. They were around 10% in each study, and corresponding p-values ranged from 0.01 to 0.06 for study 198782-004 and from 0.01 to 0.055 for study 198782-005.

When comparing results between the two studies, it is noted that although the clinical success rates for either gatifloxacin or vehicle were almost 15% higher in study 198782-004 compared to study 198782-005; the point estimates of the treatment difference were relatively consistent at around 10% in both studies.

It should be noted that both studies were powered based on the assumption of 16% treatment difference between gatifloxacin and vehicle groups in the clinical success rate. However, the observed clinical success rate was only around 10%. Thus both studies were underpowered.

Since the Applicant used LOCF approach to impute the missing values, additional sensitivity analyses were performed treating missing values as treatment failures by the statistical reviewer to examine consistency of the efficacy results. The following table presents the analyses results for both studies; these results are consistent with the primary analyses results.

Table 13: Statistical Reviewer's Sensitivity Analysis of Clinical Success Treating Missing Values as Treatment Failures

	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
Study 198782-004 Clinical Success (Day 6 Visit Analysis)	122/167 (73.1%)	100/158 (63.3%)	0.059	9.8% (-0.3%, 19.9%)
Study 198782-005 Clinical Success (Up to Day 6 Analysis)	79/166 (47.6%)	62/167 (37.1%)	0.053	10.5% (-0.09%, 21.0%)

The statistical reviewer also analyzed the clinical success rate by study day, and the results are presented in the following tables. These results indicate that majority of the patients were evaluated on study day 6 and day 7 for the Day 6 Visit (284/325 (87%) for study 198782-004 and 315/333 (95%) for study 198782-005).

Table 14: Statistical Reviewer's Sensitivity Analysis of Clinical Success by Study Day

Study 198782-004			
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**Difference**
Day 4 Visit			
Day 2	1/1 (100%)	1/1 (100%)	0
Day 3	4/16 (25%)	1/6 (16.7%)	8.3%

Day 4	48/133 (36.1%)	28/131 (21.4%)	14.7%
Day 5	3/10 (30%)	3/12 (25%)	5%
Day 6 Visit			
Day 6	83/108 (76.6%)	68/100 (68%)	8.9%
Day 7	32/43 (74.4%)	26/43 (60.5%)	13.9%
Day 8	4/5 (80%)	4/4 (100%)	-20%
Day 9	3/3 (100%)	1/1 (100%)	0
Day 10	0	0/1 (0%)	n/a
Day 11	0	0	n/a
Day 12	0	0	n/a
Day 13	0	0	n/a
Day 14	0	1/1 (100%)	n/a
Study 198782-005			
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**Difference**
Day 4 Visit			
Day 2	0	0	n/a
Day 3	1/2 (50.0%)	0/1 (0%)	50.0%
Day 4	20/153 (13.1%)	16/153 (10.5%)	2.6%
Day 5	2/5 (40.0%)	¼ (25.0%)	15.0%
Day 6 Visit			
Day 6	79/141 (56.0%)	62/137 (45.3%)	10.7%
Day 7	20/21 (95.2%)	14/16 (87.5%)	7.7%
Day 8	0	1/2 (50.0%)	n/a
Day 9	0	1/1 (100%)	n/a
Day 10	0	0/1 (0%)	n/a
Day 11	0	0	n/a
Day 12	0	0	n/a
Day 13	0	0	n/a
Day 14	0	0	n/a

To further examine the robustness of the treatment effect, the statistical reviewer analyzed the clinical success rate based on pooled data of both studies. This analysis is stratified by study. Because there was difference in terms of bacterial pathogens between the two studies and clinical success rates of the two studies were different, we do not recommend using combined analysis results as the basis of approval. The integrated efficacy results for the two studies are listed in the following table.

Table 15: Statistical Reviewer's Integrated Analysis Results of Clinical Success for Studies 198782-004 and 198782-005

	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value[1]**	**Observed Difference (95% CI[1])**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	79/333 (23.7%)	50/325 (15.4%)	0.0077	8.3% (2.2%, 14.0%)
Day 6 Visit				
Up to Day 6	193/333 (58.0%)	148/325 (45.5%)	0.0016	12.5% (4.7%, 19.8%)
Up to Day 7	218/333 (65.5%)	173/325 (53.2%)	0.0015	12.3% (4.6%, 19.4%)
Up to Day 8	222/333 (66.7%)	178/325 (54.8%)	0.0019	11.9% (4.3%, 19.0%)
Up to Day 9	224/333 (67.3%)	180/325 (55.4%)	0.0019	11.9% (4.3%, 18.9%)
Up to Day 14	224/333 (67.3%)	181/325 (55.4%)	0.0025	11.6% (4.0%, 18.6%)
Day 6 Visit	224/333 (67.3%)	181/325 (55.4%)	0.0025	11.6% (4.0%, 18.6%)

[1] p-vale and CI for Cochran-Mantel-Haenszel test stratified by study

Finally, the statistical reviewer analyzed the microbiological cure rate by study duration for each study and for both studies combined. The results are presented in the following tables. While the sensitivity analyses produce consistent point estimates for treatment difference in microbiological cure rate within each study, the point estimates for treatment difference of study 198782-004 (at around 30%) was much higher than that of study 198782-005 (at around 10%). This difference may be due to difference in the baseline bacterial pathogens between the two studies.

Table 16: Statistical Reviewer's Sensitivity Analysis Results of Microbiological Cure Rate

Study 198782-004				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
mITT (LOCF) Microbiological Cure				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	145/167 (86.8%)	81/158 (51.3%)	<0.0001	35.5% (26.2%, 44.9%)
Day 6 Visit				
Up to Day 6	148/167 (88.6%)	94/158 (59.5%)	<0.0001	29.1% (20.1%, 38.2%)

Up to Day 7	149/167 (89.2%)	97/158 (61.4%)	<0.0001	27.8% (18.9%, 36.8%)
Up to Day 8	149/167 (89.2%)	97/158 (61.4%)	<0.0001	27.8% (18.9%, 36.8%)
Up to Day 9	149/167 (89.2%)	97/158 (61.4%)	<0.0001	27.8% (18.9%, 36.8%)
Day 6 Visit	149/167 (89.2%)	97/158 (61.4%)	<0.0001	27.8% (18.9%, 36.8%)
Study 198782-005				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
mITT (LOCF) Microbiological Cure				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	146/166 (88.0%)	123/167 (73.7%)	0.0009	14.3% (6.0%, 22.6%)
Day 6 Visit				
Up to Day 6	153/166 (92.2%)	134/167 (80.2%)	0.0016	11.9% (4.6%, 19.2%)
Up to Day 7	155/166 (93.4%)	135/167 (80.8%)	0.0006	12.5% (5.5%, 19.6%)
Up to Day 8	155/166 (93.4%)	135/167 (80.8%)	0.0006	12.5% (5.5%, 19.6%)
Up to Day 9	155/166 (93.4%)	135/167 (80.8%)	0.0006	12.5% (5.5%, 19.6%)
Up to Day 10	155/166 (93.4%)	136/167 (81.4%)	0.001	11.9% (4.9%, 18.9%)
Day 6 Visit	155/166 (93.4%)	136/167 (81.4%)	0.001	11.9% (4.9%, 18.9%)

Table 17: Statistical Reviewer's Integrated Analysis Results of Microbiological Cure for Studies 198782-004 and 198782-005

	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value[1]**	**Observed Difference (95% CI[1])**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	291/333 (87.4%)	204/325 (62.8%)	<0.0001	24.6% (18.6%, 31.0%)
Day 6 Visit				
Up to Day 6	301/333 (90.4%)	228/325 (70.2%)	<0.0001	20.2% (14.6%, 26.2%)
Up to Day 7	304/333 (91.3%)	232/325 (71.4%)	<0.0001	19.9% (14.4%, 25.8%)
Up to Day 8	304/333 (91.3%)	232/325 (71.4%)	<0.0001	19.9% (14.4%, 25.8%)

Up to Day 9	304/333 (91.3%)	232/325 (71.4%)	<0.0001	19.9% (14.4%, 25.8%)
Up to Day 10	304/333 (91.3%)	233/325 (71.7%)	<0.0001	19.6% (14.1%, 25.4%)
Day 6 Visit	304/333 (91.3%)	233/325 (71.7%)	<0.0001	19.6% (14.1%, 25.4%)

[1] p-vale and CI for Cochran-Mantel-Haenszel test stratified by study

3.2 Evaluation of Safety

The following tables summarized adverse events (AEs) for Study 198782-004 and 198782-005 respectively.

Table 18: Ocular Aes or any Aes in >1% of subjects in either group for study 198782-004 (Safety Population)

Adverse Event	Gatifloxacin (n = 288)	Vehicle (n = 289)
Conjunctivitis bacterial	14 (4.9%)	13 (4.5%)
Pyrexia	4 (1.4%)	1 (0.3%)
Pharyngolaryngeal pain	3 (1.0%)	1 (0.3%)
Conjunctivitis	2 (0.7%)	4 (1.4%)
Headache	2 (0.7%)	3 (1.0%)
Eyelid oedema	2 (0.7%)	3 (1.0%)
Eye pruritus	1 (0.3%)	4 (1.4%)
Lacrimation increased	1 (0.3%)	4 (1.4%)
Otitis media	0 (0.0%)	3 (1.0%)
Visual acuity reduced	0 (0.0%)	2 (0.7%)

Source: Sponsor's study 197782 report Tables 12-3 and 12-4.

Table 19: Ocular Aes or any Aes in >1% of subjects in either group for study 198782-005 (Safety Population)

Adverse Event	Gatifloxacin (N = 429)	Vehicle (N = 427)
Eye irritation	14 (3.3%)	7 (1.6%)
Dysgeusia	8 (1.9%)	1 (0.2%)
Eye pain	6 (1.4%)	8 (1.9%)
Conjunctivitis bacterial	5 (1.2%)	19 (4.4%)
Instillation site irritation	5 (1.2%)	0 (0.0%)
Conjunctivitis	0 (0.0%)	5 (1.2%)
Corneal epithelium defect	1 (0.2%)	0 (0%)
Iritis	1 (0.2%)	0 (0%)
Keratitis viral	1 (0.2%)	0 (0%)
Punctate keratitis	1 (0.2%)	0 (0%)
Adenovirus infection	0 (0%)	1 (0.2%)
Corneal erosion	0 (0%)	1 (0.2%)

Hordeolum	0 (0%)	1 (0.2%)

Source: Sponsor's study 198782-005 report Tables 12-3 and 12-6

Please see the review of the medical officer for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study 198782-004

The primary endpoints were analyzed by subgroups on age, gender, and race for study 198782-004. The clinical success rate results for the subpopulations are highly variable. Male subjects had much higher clinical success rate than female subjects; subjects between 1 and 18 years old had higher clinical success rate than subjects older than 18 years; and Hispanic subjects had much higher clinical success rate (see Table 19).

Table 20: Study 198782-004 Analyses of Primary Endpoints by Age, Gender, and Race

Clinical Success					
	Gatifloxacin (A) (N=167) Observed Response		**Vehicle (B) (N=158) Observed Response**		**Observed Differences (A-B)**
	n/m	%	n/m	%	%
Gender					
Male	67/83	80.7	46/74	62.2	18.6
Female	58/84	69.1	57/84	67.9	1.2
Age					
1-18	70/81	86.4	55/82	67.1	19.5
19 – 65	36/53	67.9	41/65	63.1	4.8
> 65 years	19/33	57.6	7/11	63.6	-6.0
Race					
Caucasian	62/84	73.8	59/84	70.2	3.6
Asian	2/3	66.7	5/7	71.4	-4.7
African American	7/12	58.3	7/10	70.0	-11.7
Hispanic	52/66	78.8	29/51	56.9	21.9
Other	2/2	100.0	3/6	50.0	50.0
Microbiological Cure					
	Gatifloxacin (A) (N=167) Observed Response		**Vehicle (B) (N=158) Observed Response**		**Observed Differences (A-B)**
	n/m	%	n/m	%	%
Gender					
Male	76/83	91.6	50/74	67.6	24
Female	73/84	86.9	47/84	56.0	30.9

Age					
1-18	72/81	88.9	44/82	53.7	35.2
19 – 65	47/53	88.9	46/65	70.8	17.9
> 65 years	30/33	90.9	7/11	63.6	27.3
Race					
Caucasian	77/84	91.7	56/84	66.7	25.0
Asian	3/3	100.0	5/7	71.4	28.6
African American	8/12	66.7	5/10	50.0	16.7
Hispanic	59/66	89.4	27/51	52.9	36.5
Other	2/2	100.0	4/6	66.7	33.3

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.

4.2 Study 198782-005

The primary endpoints were analyzed by subgroups on age, gender, and race for study 198782-005 as well. In general, there were no marked differences in the efficacy results among the various subpopulations (see Table 20).

Table 21: Study 198782-005 Analyses of Primary Endpoints by Age, Gender, and Race

Clinical Success					
	Gatifloxacin (A) (N=166) Observed Response		**Vehicle (B) (N=167) Observed Response**		**Observed Differences (A-B)**
	n/m	%	n/m	%	%
Gender					
Male	51/88	58.0	43/100	43.0	15.0
Female	48/78	61.5	35/67	52.2	9.3
Age					
1-18	20/21	95.2	15/21	71.4	23.8
19-65	117/125	93.6	106/124	85.5	8.1
> 65 years	18/20	90.0	15/22	68.2	21.8
Race					
Caucasian	3/3	100.0	3/3	100.0	0.0
Asian	86/153	56.2	67/151	44.4	11.8
African American	1/1	100.0	2/3	66.7	33.3
Hispanic	9/9	100.0	6/10	60.0	40.0
Microbiological Cure					
	Gatifloxacin (A) (N=166) Observed Response		**Vehicle (B) (N=167) Observed Response**		**Observed Differences (A-B)**
	n/m	%	n/m	%	%
Gender					
Male	84/88	95.5	84/100	84.0	11.5

Female	71/78	91.0	52/67	77.6	13.4
Age					
1-18	20/21	95.2	15/21	71.4	23.8
19-65	117/125	93.6	106/124	85.5	8.1
> 65 years	18/20	90.0	15/22	68.2	21.8
Race					
Caucasian	3/3	100.0	2/3	66.7	33.3
Asian	143/153	93.5	127/151	84.1	9.4
African American	1/1	100.0	1/3	33.3	66.7
Hispanic	8/9	88.9	6/10	60.0	28.9

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.

4.3 Sensitivity Analysis Excluding Site 10008 from Study 198782-004

For study 198782-004, DSI inspector raised the following concerns regarding site 10008 (Principal Investigator: Dr. Daniel A. Long; Sub-Investigator: (b) (4) for this site) in the inspection report:
"Subjects were enrolled in the study and randomized prior to the completion of the tests to determine eligibility for enrollment. Subjects were dosed with study medication prior to randomization and study drug assignment. The inspection also revealed that study source documents and clinic charts contained unexplained and uncorroborated changes in the data. These changes resulted in making subjects appear to meet the inclusion criteria for the study or resulted in the documentation of protocol compliance. Study source records were missing for two subjects enrolled in the study. Source documents contained changes in the data made by Dr. (b) (4) that were initially recorded by Dr. Long. These changes were made during monitoring visits and resulted in the documentation of protocol compliance."

To address this DSI inspection issue, the statistical reviewer performed additional sensitivity analyses excluding the site in question; the following table presents the analysis results for the clinical success and microbiological cure. The sensitivity analysis results are more favorable to the test drug compared to the original primary analysis results including site 10008.

Table 22: Statistical Reviewer's Analysis Results of Clinical Success and Microbiological Cure for Study 198782-004 Excluding Site 10008 (LOCF)

	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
Clinical Success (Day 6 Visit Analysis)	117/153 (76.5%)	91/144 (65.2%)	0.013	13.3% (2.9%, 23.6%)
Microbiological Cure (Day 6 Visit Analysis)	139/153 (90.9%)	85/144 (59.0%)	<0.0001	31.8% (22.6%, 41.1%)

4.4 Sensitivity Analysis Including Site 13020 from Study 198782-005

The Applicant had serious concerns about data integrity at one Indian site (site 13020). Of 72 patients randomized at that site, no one discontinued due to adverse events or was lost to follow-up. Therefore site 13020 was excluded from the primary analyses by the Applicant. The Applicant communicated with FDA regarding concerns of data integrity for this site in January 2009. According to the Applicant, the decision of efficacy analyses excluding data from that site was prior to database lock.

The efficacy results including data from site 13020 were analyzed by the Applicant as sensitivity analyses and are presented in the following table. The results are relatively consistent with the analysis results excluding site 13020.

Table 23: Sponsor's Analysis Results of Clinical Success for Study 198782-005 Including Site 13020 (LOCF)

	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
Clinical Success (Up to Day 6 Analysis)	97/179 (54.2%)	84/185 (45.4%)	0.094	8.8% (-1.5%, 19.0%)
Clinical Success (Day 6 Visit Analysis)	111/179 (62.0%)	94/185 (50.8%)	0.031	11.2% (1.1%, 21.3%)

Source: Sponsor's study 198782-005 report Tables 14.2-8.1 and 14.5-30.1

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are no major statistical issues for studies 198782-004 and 198782-005. However, the primary efficacy results for both studies were statistically marginal with p-values slightly above the 0.05 significance level: p-value = 0.057 for study 198782-004, and p-value = 0.055 for study 198782-005.

To further examine the robustness of the efficacy results, the statistical reviewer performed additional sensitivity analyses using different study durations (from Day 4 Visit to the day that last patient came in for Visit 3 evaluation); the results are presented in the following table, where the shaded rows are the primary efficacy results. Although the clinical success rates for either gatifloxacin or vehicle were almost 15% higher in study 198782-004 compared to study 198782-005, the point estimates of the treatment difference were relatively consistent and around 10% in both studies.

It should be noted that both studies were powered based on the assumption of 16% treatment difference between gatifloxacin and vehicle groups in the clinical success rate. However, the observed clinical success rate was only around 10%. Thus both studies were underpowered.

Table 24: Statistical Reviewer's Sensitivity Analysis of Clinical Success

Study 198782-004				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	56/167 (33.5%)	33/158 (20.9%)	0.010	12.6% (3.1%, 22.2%)
Day 6 Visit				
Up to Day 6	107/167 (64.1%)	79/158 (50.0%)	0.010	14.1% (3.4%, 24.7%)
Up to Day 7	119/167 (71.3%)	97/158(61.4%)	0.060	9.9% (-0.3%, 20.1%)
Up to Day 8	123/167 (73.7%)	101/158 (63.9%)	0.058	9.7% (-0.3%, 19.8%)
Up to Day 9	125/167 (74.9%)	102/158 (64.6%)	0.044	10.3% (0.4%, 20.2%)
Up to Day 14	125/167 (74.9%)	103/158 (65.2%)	0.057	9.7% (-0.3%, 19.6%)
Day 6 Visit	125/167 (74.9%)	103/158 (65.2%)	0.057	9.7% (-0.3%, 19.6%)
Study 198782-005				
	Gatifloxacin n/N (%)	**Vehicle** n/N (%)	**p-value[1]**	**Difference (95% CI)**
mITT (LOCF) Clinical Success				
Day 4 Visit (Day 4 ± 1)				
Up to Day 5	23/166 (13.9%)	17/167 (10.2%)	0.30	3.7% (-3.3%, 10.7%)
Day 6 Visit				
Up to Day 6	86/166 (51.8%)	69/167 (41.3%)	0.055	10.5% (-0.2%, 21.2%)
Up to Day 7	99/166 (59.6%)	76/167 (45.5%)	0.010	14.1% (3.5%, 24.8%)
Up to Day 8	99/166 (59.6%)	77/167 (46.1%)	0.014	13.5% (2.9%, 24.2%)
Up to Day 9	99/166 (59.6%)	78/167 (46.7%)	0.018	12.9% (2.3%, 23.6%)
Day 6 Visit	99/166 (59.6%)	78/167 (46.7%)	0.018	12.9% (2.3%, 23.6%)

5.2 Conclusions and Recommendations

In study 198782-004, for the pre-defined primary analysis of Day 6 analysis (including all data collected for the day 6 visit, even if it was collected after day 6), the clinical resolution rate for gatifloxacin 0.5% ophthalmic solution vs. Vehicle was 74.9% (125/167) vs. 65.2% (103/158), a 9.7% treatment difference with 95% confidence interval of (-0.3%, 19.6%) (p-value = 0.057). The study result was statistically marginal and the p-value was slightly above the 0.05 significance level.

In study 198782-005, for the pre-defined primary analysis of up to Day 6 analysis (using only data collected up to and including day 6), the clinical resolution rate for gatifloxacin 0.5% ophthalmic solution vs. Vehicle was 51.8% (86/166) vs. 41.3% (69/167), a 10.5% treatment difference with 95% confidence interval of (-0.2%, 21.2%) (p-value = 0.055). The study result was also statistically marginal and the p-value was slightly above the 0.05 significance level.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22548	ORIG-1	ALLERGAN	GATIFLOXACIN OPHTHALMIC SOLUTION 0.5%

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/s/

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03/26/2010

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