CLINICAL REVIEW

Application Type	NDA
Submission Number	22-548
Submission Code	Original
Letter Date	7/30/2009
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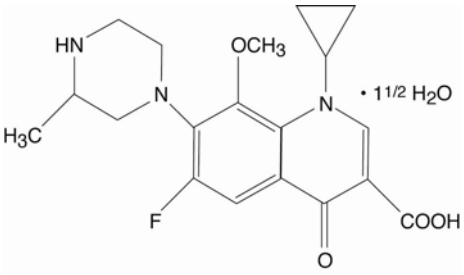
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	4/13/2010
Established Name	gatifloxacin ophthalmic solution, 0.5%
(Proposed) Trade Name	Zymaxid
Therapeutic Class	anti-infective, fluoroquinolone
Applicant	Allergan, Inc. 2525 Dupont Drive Irvine, CA 92612
Priority Designation	S

Formulation ($C_{19}H_{22}FN_3O_4 \cdot 1½H_2O$)



Proposed Dosing Regimen

Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times.
Days 2 through 5: Instill one drop two times daily in the affected eye(s) while awake, approximately 12 hours apart.

Proposed Indication

Treatment of the signs and symptoms of bacterial conjunctivitis

Intended Population

Patients 1 year of age or older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended from a clinical perspective that NDA 22-548, Zymaxid (gatifloxacin ophthalmic solution) 0.5% be approved for the treatment of bacterial conjunctivitis with labeling revisions listed in this review.

The dosing recommendation is for 7 days as is standard for topical ophthalmic anti-infective products.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Zymaxid when dosed eight times on day 1 followed by two to four times a day for days 2 through 7 is superior to its vehicle in the treatment of bacterial conjunctivitis.

1.2 Risk Benefit Assessment

Efficacy of the drug substance, gatifloxacin, has been demonstrated in multiple systemic indications in prior NDA submissions. Gatifloxacin ophthalmic solution 0.5% was studied in two adequate and well controlled studies submitted in this NDA. The clinical success results of gatifloxacin compared to vehicle in each of these studies were marginally statistically significant in the prespecified analyses. Sensitivity analyses demonstrated that the clinical success results to be convincingly statistically significant. Microbiological cure rates for gatifloxacin ophthalmic solution 0.5% were also superior to vehicle in both trials.

In Study 198782-004, the primary analysis was the Day 6 visit analysis in the modified Intent-to-Treat population. This analysis included all data collected for the day 6 visit even if collected after study day 6. The primary efficacy variable, clinical success defined as achievement of a score of zero for both conjunctival hyperemia and conjunctival discharge in the study eye, was marginally statistically significant when comparing the gatifloxacin and vehicle treatment groups. The Up-to-Day 6 visit sensitivity analysis was performed including 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 in the modified Intent-to-Treat population in the modified Intent-to-Treat population. In this analysis, the primary efficacy variable, clinical success was convincingly statistically significant.

Prior to unblinding the data for Study 198782-005, the Applicant revised the primary efficacy analysis for Study 005 to correspond with the more successful Up-to-Day 6 visit analysis in Study 004. In Study 198782-005, the treatment group difference in the proportion of patients achieving clinical success was only marginally statistically significant in the Up to Day 6 visit analysis. The results in the Day 6 visit analysis for the primary efficacy variable as originally planned, clinical success at day 6 were convincingly statistically significant in favor of gatifloxacin.

Relative safety of gatifloxacin ophthalmic solution 0.5% was demonstrated in the two submitted adequate and well controlled studies. The most frequently reported adverse events were: worsening of the conjunctivitis, eye irritation, dysgeusia, eye pain, pyrexia, instillation site irritation, pharyngolaryngeal pain, headache and eye edema. No new safety concerns regarding the use of gatifloxacin for the treatment of bacterial conjunctivitis were raised in this NDA submission.

The benefit of gatifloxacin ophthalmic solution 0.5% in the treatment of bacterial conjunctivitis has been demonstrated in this NDA application. The risk for using this drug is mild and is consistent with the currently marketed Zymar. The risk/benefit profile has been adequately established.

1.3 Recommendations for Postmarket Risk Management Activities

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Studies/Clinical Trials

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

Gatifloxacin is a fourth generation 8-methoxy fluoroquinolone that inhibits DNA gyrase and topoisomerase IV. Allergan's NDA 21-493 for Zymar (gatifloxacin ophthalmic solution) 0.3% was approved in March 2003 for the indication of bacterial conjunctivitis in adults and pediatric patients above the age of 1 year. In this NDA, Zymar (gatifloxacin ophthalmic solution) 0.3% has been reformulated with a higher concentration of gatifloxacin, 0.5%. The excipients are the same in both formulations. The formulations are identical apart from the increased drug substance concentration, a small reduction in pH to insure adequate solubility of the drug substance and a slightly lower sodium chloride concentration for tonicity.

2.1 Product Information

Established Name:	gatifloxacin ophthalmic solution 0.5%
Proposed Trade Name:	ZYMAXID
Chemical Class:	new strength, new dosing regimen
Pharmacological Class:	fluoroquinolone
Indication:	treatment of bacterial conjunctivitis

Dosing Regimen: Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times.

Days 2 through 5: Instill one drop two times daily in the affected eye(s) while awake, approximately 12 hours apart.

Age Groups: Patients 1 year of age or older:

2.2 Tables of Currently Available Treatments for Proposed Indications

Ophthalmic products currently approved for the treatment of bacterial conjunctivitis include azithromycin ophthalmic solution, ciprofloxacin ophthalmic solution, erythromycin ophthalmic ointment, gatifloxacin ophthalmic solution, gentamicin ophthalmic solution, levofloxacin ophthalmic solution, moxifloxacin ophthalmic solution, norfloxacin ophthalmic solution, ofloxacin ophthalmic solution, and tobramycin ophthalmic solution.

2.3 Availability of Proposed Active Ingredient in the United States

In March 2003, gatifloxacin ophthalmic solution 0.3% was approved in Allergan's NDA 21-493 for Zymar. It is currently being marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no specific issues that need to be addressed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original protocol for Study 198782-004 was submitted as a Special Protocol Assessment (SPA) to the Agency for review in an amendment to IND 59,408 on 28 March 2007. Agency comments were provided to Allergan in a written correspondence from the Agency dated 11 May 2007 and 25 July 2007. After additional correspondence, the final protocol was amended to comply with the Agency comments and filed to the IND on 3 August 2007.

2.6 Other Relevant Background Information

Zymaxid (gatifloxacin ophthalmic solution) 0.5% is not marketed in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information requests for the sponsor.

3.2 Compliance with Good Clinical Practices

On January 14, 2009, Allergan notified the FDA of significant cGCP violations at a study site in India in Study 198782-005. The investigator at this site was Shanta Motwane, MD. At Site 13020 was found to have significant data integrity issues. This site enrolled 72 patients, of whom 31 were included in the mITT population. At Site 13020, the clinical success rates in both groups at the day 6 time point in the mITT population using the up to day 6 analysis method (84.6% [11/13] in the gatifloxacin group and 83.3% [15/18] in the vehicle group) were somewhat higher than at most other sites with comparable enrollment.

During monitoring of the site, significant cGCP violations were observed. These violations involved source documentation anomalies which in the sponsor's judgment did not adequately support the data in the Case Report Forms. In contrast to other study sites, this site reported no adverse events, concomitant medications, and/or medical/ophthalmic history for any randomized patients. As such Allergan is concerned the site was not sufficiently diligent in querying the patients for safety and history information. Allergan is concerned about the data quality at the site.

Allergan proposed excluding all of the study data at this site. In the 198782-005 clinical study report; data without this site will be presented in the body of the report; analyses of the primary efficacy variable (clinical success) and adverse events with that site will be presented as supplemental. Allergan proposes to analyze the data without this site for the integrated summaries of safety and efficacy.

Reviewer's Comment:
The Agency concurred with excluding all data from Site 13020. All efficacy analyses are presented without data from Site 13020 included.

3.3 Financial Disclosures

Allergan has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for gatifloxacin ophthalmic solution 0.5%. There is one investigator who participated in the phase (b) (6) safety and efficacy trials who had disclosed financial ties to the sponsor.

Investigators with financial Interests or Arrangements

Clinical Study	Investigators
198782-004	(b) (6)
198782-005	None

Reviewer's Comment:
A review of these arrangements does not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Gatifloxacin ophthalmic solution 0.5% (9416X) in this submission is a clear, pale yellow, sterile, preserved, and isotonic aqueous solution packaged in a multidose eye-drop bottle. The drug substance (DS), gatifloxacin sesquihydrate, is a fluoroquinolone antibacterial agent. The proposed drug product contains 0.5% w/v gatifloxacin sesquihydrate as the Drug Substance (DS). Gatifloxacin sesquihydrate is the same DS and comes from the same supplier as is currently approved in ZYMAR (gatifloxacin ophthalmic solution) 0.3% in NDA 21-493.

It has been reformulated at a higher concentration.

Specifications of Gatifloxacin Drug Substance

Test (Method #)	Specifications
	(b) (4)

Reviewer's Comment:
The drug substance specifications are the same as those for Zymar (gatifloxacin ophthalmic solution) 0.3%.

Composition of Gatifloxacin Ophthalmic Solution 0.5%

Component	Grade	Function	Concentration
Gatifloxacin Sesquihydrate (%w/v)	N/A	Active ingredient	0.5
Benzalkonium Chloride (%w/v)			0.005
Edetate Disodium (% w/v)			
Sodium Chloride (%w/v)			
Hydrochloric Acid or Sodium Hydroxide	NF/Ph Eur	pH adjustment	
Purified water	USP/Ph Eur		

Reviewer's Comment:
The composition of gatifloxacin ophthalmic solution 0.5% differs from that of Zymar (gatifloxacin ophthalmic solution) 0.3% in that the drug concentration is increased, pH is reduced to ensure solubility of the drug substance, and the sodium chloride concentration is decreased slightly for tonicity.

4.2 Clinical Microbiology

From the Clinical Microbiology review:

> From the clinical microbiology perspective, this NDA submission may be approved, provided that the Applicant makes the changes in the microbiology subsection of the proposed label recommended by the Agency (below).
>
> In the Indications and Usage section (Section 1) and in the Microbiology section (Section 12.4), [redacted] are removed from the list of bacteria for which ZYMAXID™ is indicated. The Applicant has reported no experience with these organisms in subjects treated in clinical trials performed in the United States, and has presented no data from in vitro studies to support inclusion in the proposed label.

For additional information, refer to Sections 6.1 and 6.2.

4.3 Preclinical Pharmacology/Toxicology

Gatifloxacin has been previously characterized and information regarding the nonclinical pharmacology, pharmacokinetics and toxicology is referenced to NDA 21-493 for ZYMAR (gatifloxacin ophthalmic solution) 0.3%.

A favorable safety profile was established in nonclinical toxicity studies conducted in support of the marketed product Zymar (gatifloxacin ophthalmic solution) 0.3% submitted in NDA 21-493. Additionally, a favorable safety profile of a lower gatifloxacin concentration of 0.3%, but with an increased topical ocular dosing frequency of four times per day, has been established in

humans with Zymar. In a phase 1 study, two drops of 0.3% and 0.5% gatifloxacin administered once for one day, four times per day for 7 days, or eight times per day for three days were well tolerated in healthy subjects. No additional nonclinical studies were conducted in support of the reformulated 0.5% gatifloxacin ophthalmic formulation.

4.4 Clinical Pharmacology

Gatifloxacin has been previously characterized and information regarding the nonclinical pharmacology, pharmacokinetics and toxicology is referenced to NDA 21-493 for ZYMAR (gatifloxacin ophthalmic solution) 0.3%. In addition, one nonclinical pharmacokinetic study comparing the ocular pharmacokinetics of gatifloxacin ophthalmic solution 0.3% QID versus gatifloxacin ophthalmic solution 0.5% BID was conducted in Dutch-Belted rabbits (Report PK-08-P029-PK).

4.4.1 Mechanism of Action

The mechanism of action for gatifloxacin was previously submitted and evaluated as part of the Zymar NDA (NDA 21-493). Gatifloxacin is an 8-methoxyfluoroquinolone with in vitro activity against both gram negative and gram positive microorganisms. The antibacterial action results from inhibition of the DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

4.4.2 Pharmacodynamics

Refer to the Clinical Pharmacology review.

4.4.3 Pharmacokinetics

Refer to the Clinical Pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
198782-004 Safety and Efficacy Study	Randomized, double-masked, vehicle-controlled, parallel group, 2-arm, multicenter	Patients at least 1 year of age with acute bacterial conjunctivitis	Gatifloxacin 0.5% ophthalmic solution Vehicle	Day 1: 1 drop 8 up to 8 times Days 2 – 5: 1 drop BID	5 days with evaluation on following day	578
198782-005 Safety and Efficacy Study						859

5.2 Review Strategy

This application contains two identical safety and efficacy trials to support the approval of gatifloxacin ophthalmic solution, 0.5% for the treatment of bacterial conjunctivitis. The studies were randomized, multicenter, double-masked, vehicle-controlled, two-arm and parallel group in design. The individual studies differed in the definition of the primary efficacy endpoint.

The submitted clinical study reports, clinical protocols, and literature reports related to Studies 198782-004 and 198782-005 were reviewed in depth. The majority of the application was submitted in electronic CTD format. Modules 1, 2, and 5 were reviewed in depth.

5.3 Discussion of Individual / Clinical Studies

5.3.1 **Study 198782-004:** A 6 Day, Phase 3, Multicenter, Randomized, Double-masked, Parallel Study to Compare the Safety and Efficacy of Gatifloxacin 0.5% Ophthalmic Solution BID with that of Vehicle in the Treatment of Acute Bacterial Conjunctivitis

Study Design

This was a 6-day, multicenter, double-masked, randomized, 2-arm, vehicle controlled, parallel-group study comparing gatifloxacin ophthalmic solution 0.5% with that of gatifloxacin vehicle for the treatment of acute bacterial conjunctivitis in patients older than 1 year of age.

Table 5.3.1-1 Primary Efficacy Endpoint Comparison

Study	Primary Efficacy Endpoint
198782-004	Clinical success in the study eye in the ITT population (randomized patients with a positive baseline culture).
198782-005	Clinical success in the study eye using data up to day 6 in the ITT population (randomized patients with or without a positive baseline culture)

Qualified patients were randomly assigned to either gatifloxacin 0.5% or gatifloxacin vehicle in an even allocation (1:1). At baseline (day 1), patients in both treatment groups were instructed to put one drop of study medication in each qualified eye every 2 hours up to 8 times total. On days 2 through 5, patients in both treatment groups were instructed to put 1 drop of the assigned study medication in each qualified eye twice daily. If an unqualified eye (an eye that was not clinically diagnosed on day 1) was clinically diagnosed with bacterial conjunctivitis prior to the day 6 visit, the patient was assigned a new bottle of identically masked study medication with which to treat the unqualified eye with 1 drop every 2 hours up to 8 times on the day of diagnosis and twice daily thereafter. The duration of treatment for the unqualified eye was left to the discretion of the investigator but was not to exceed 5 days. If an unqualified eye was clinically diagnosed with bacterial conjunctivitis at day 6, the patient was to exit the study and receive clinical standard of care.

This study 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. Ocular symptoms were assessed, visual acuity was measured, biomicroscopy was performed, and a conjunctival sample for bacterial culture and sensitivity (qualified eye) was obtained at each of those visits. Adverse events and concomitant medications and procedures were reviewed at each visit. An Unqualified Eye Follow-up visit was completed by patients who were clinically diagnosed with bacterial conjunctivitis after the day 1 visit and prior to the day 6 visit. The Unqualified Eye Follow-up visit was considered the exit visit for these patients.

Table 5.3.1-2 Schedule of Procedures and Assessments

	Scheduled Visits			
			Exit	
	Day 1 (Baseline)	Day 4	Day 6 [a]	Unqualified Eye Follow-up [b]
Informed consent and privacy forms	X			
Urine pregnancy test, if applicable	X			
Demographics, Medical and ophthalmic history, Prior Medications, Ophthalmoscopy	X			
Visual acuity	X	X	X	X [c]
Biomicroscopy	X	X	X	X [c]
Ocular sign and symptom assessment	X	X	X	X [c]
Conjunctival sample for bacterial culture and sensitivity (qualified eye(s)) [d]	X	X	X	
Conjunctival sample for adenovirus antigen (qualified eye (s)) [e]	X			
Conjunctival sample for bacterial culture and sensitivity (unqualified eye)		X [f]		X [f]
Conjunctival sample for adenovirus antigen (unqualified eye)		X [g]		
Serious medical events	X			
Randomization	X			
Drug instillation (times/day)	q2h [h]	BID [i]		
Review of adverse events	X	X	X	X
Review of concomitant medications / concurrent procedures	X	X	X	X
Distribution of study medication	X	X [J]		
Collection of unused study drug			X	X

a Occurred 12 to 48 hours after the last dose of study medication was administered in the qualified eye(s). This was the exit visit for patients who did not become clinically diagnosed with bacterial conjunctivitis in an unqualified eye before the day 6 visit.
b After last dose of study medication. The exit visit for patients who became clinically diagnosed with bacterial conjunctivitis in an unqualified eye after the day 1 visit and before the day 6 visit.
c Only the unqualified eye was evaluated during this visit.
d At baseline obtained prior to the instillation of study medication and at day 4 at least 4 hours after the last administration of study drug.
e Taken after collection of conjunctival sample(s) for bacterial culture and sensitivity and before any study medication was administered.
f Obtained prior to instillation of study medication in the unqualified eye if that eye became clinically diagnosed with bacterial conjunctivitis after the day 1 visit and before the day 6 visit.
g Only if an unqualified eye became clinically diagnosed with bacterial conjunctivitis after the day 1 visit and before the day 6 visit. This was performed following the collection of conjunctival sample(s) for bacterial culture and sensitivity and before any ophthalmic drops were administered. If the adenovirus antigen test was positive, the patient exited the study.
h Dosing on day 1 did not exceed a total of 8 times. The first dose was administered at the study site.
i On day 2 through 5, dosing was to occur in the morning and evening approximately 12 hours apart.
j Only if unqualified eye was clinically diagnosed with bacterial conjunctivitis.

Study Population
For enrollment into the study, each patient had to meet all of the following inclusion criteria and none of the following exclusion criteria.

Inclusion Criteria

1. Male or female ≥ 1 year of age, in good general health
2. Written informed consent obtained from the patient or his/her legally authorized representative
3. Clinically diagnosed with acute 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).
4. Patient had corrected visual acuity score equivalent to a Snellen acuity of 20/80 or better in at least one eye using a logarithmic visual acuity chart or other age-appropriate measurement method in accordance with the America Academy of Pediatrics Eye Examination and Vision Screening in Infants, Children, and Young Adults Policy Statement. The American Academy of Pediatrics Recommendations for Preventative Pediatric Health Care states that formal vision screening should begin at 3 years of age. Visual acuity measurement could be attempted for children under 3 at the discretion of the investigator. If not conducted, the child must have been able to fix and follow. Visual acuity was to be measured using the same method for each patient at each visit.
5. The patient and/or the patient's legally authorized representative were capable of understanding and were likely to complete all required visits and procedures.
6. Written Authorization for Use and Release of Health and Research Study Information was obtained from the patient or his/her legally authorized representative.
7. There was a negative urine pregnancy test result at baseline for females of childbearing potential.

Exclusion Criteria

1. Uncontrolled systemic disease
2. Known immunosuppression
3. Any serious current systemic infection
4. Females who were pregnant, nursing, or planning a pregnancy, or females who were of childbearing potential and not using a reliable means of contraception
5. Use of systemic or topical ophthalmic antibiotics within 1 week prior to the baseline visit or the anticipated use of systemic antibiotics during the study
6. Treatment with ophthalmic or systemic (oral, intravenous, or parenteral) corticosteroids during the previous 2 weeks
7. Signs and/or symptoms of conjunctivitis for more than 96 hours
8. Conjunctivitis signs and/or symptoms suggestive of fungal, viral, chlamydial, or allergic etiology

9. A positive test result for adenovirus antigen with the RPS Adeno Detector® rapid screening kit from the clinically diagnosed (qualified) eye(s)
10. Less than 2+ (moderate) conjunctival hyperemia
11. Clinical diagnosis of orbital cellulitis, pre-septal cellulitis or ulcerative keratitis, based on slit lamp examination and positive fluorescein staining.
12. Infectious blepharitis as the primary cause of ocular hyperemia and discharge in the opinion of the investigator.
13. Known allergy, sensitivity or poor tolerance to nalidixic acid, any quinolone, or any of the study medication components.
14. Anticipated wearing of contact lenses during the study
15. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
16. Any condition or situation which in the investigators opinion might put the patient at a significant risk, might confound the study results, or might interfere significantly with the patient's participation in the study
17. Any other ocular infection other than bacterial conjunctivitis (or blepharo-conjunctivitis)
18. Use of preserved topical ophthalmic medications/solutions within 3 hours prior to the first bacterial culture or the anticipated use of preserved topical ophthalmic medications/solutions during the study (except topical anesthetic used prior to the conjunctival sample tested for adenovirus antigen).

Identity of Investigational Product

Topical gatifloxacin ophthalmic solution 0.5% (Allergan formulation number 9416X) contains gatifloxacin sesquihydrate 0.5%, sodium chloride, edetate disodium, purified water and benzalkonium chloride 0.005%. It may contain hydrochloric acid and/or sodium hydroxide to adjust the pH. The product has a fill volume of 5 mL in a 10 mL bottle.

Topical gatifloxacin vehicle (Allergan formulation number 9414X) contains sodium chloride, edetate disodium, purified water and benzalkonium chloride 0.005%. It may contain hydrochloric acid and/or sodium hydroxide to adjust the pH. The product has a fill volume of 5 mL in a 10 mL bottle.

Prior and Concomitant Therapy

Prior Medications or Treatments

Medications taken within 30 days prior to baseline were recorded. Use of systemic or topical ophthalmic antibiotics within 1 week prior to the baseline visit, or use of ophthalmic or systemic (oral, IV, or parenteral) corticosteroids during the prior 2 weeks were prohibited. Participation in an investigational drug or device study within 30 days of entry into this study was prohibited. Preserved topical ophthalmic medications or solutions could not be used within three hours prior to the first bacterial culture.

Permissible Medications or Treatments

Therapy that was considered necessary for the patient's welfare was given at the discretion of the investigator. Concomitant medications and treatments were recorded on the eCRF.

Prohibited Medications or Treatments

The use of any ocular medications or ocular treatments other than the study medication (or topical anesthetic used prior to conjunctival sampling for adenovirus antigen) was prohibited. The use of systemic antibiotics and systemic corticosteroids was prohibited.

The decision to administer a prohibited medication/treatment was made with the safety of the study participant as the primary consideration. When possible, Allergan was notified before the prohibited medication/treatment was administered.

Concurrent enrollment in another clinical investigational medicinal product or device study was prohibited.

Primary Efficacy Variable

The primary efficacy variable was clinical success, defined as clearing (i.e., score = 0) of both conjunctival hyperemia and conjunctival discharge in the study eye. The primary efficacy endpoint was clinical success at day 6.

Conjunctival hyperemia and conjunctival discharge were measured on a 4-point scale (0= none, 1= mild, 2= moderate, 3= severe) at each visit.

Secondary Efficacy Variables

The secondary efficacy variables were microbiological cure and clinical improvement. A conjunctival sample for bacterial culture and sensitivity was obtained from the qualified eye(s) at each visit, and was used to determine microbiological cure and microbiological response. Microbiological cure was a secondary efficacy variable. A patient was considered to have microbiological cure if all bacterial species present at day 1 (baseline) were eradicated. Definitions for microbiological response are shown below.

Table 5.3.1-3 Microbiological Response Definitions

Eradication	The pathogen, originally present above threshold at baseline, is absent in the follow-up culture
Reduction	The pathogen, originally present above threshold at baseline, is reduced to a count below threshold in the follow-up culture
Persistence	The pathogen, originally present above threshold at baseline, is reduced to a count below baseline count, but is above or equal to threshold in the follow-up culture
Proliferation	The pathogen, originally present above threshold at baseline, is increased to a count above baseline count in the follow-up culture

Reviewer's Comment:
Microbiological eradication of all bacterial species present at Day 1 on Day 6 is the only clinically relevant and acceptable microbiological endpoint. Other measures of 'microbiological response' as defined above are not clinically relevant.

Although the results were not included in efficacy analyses, if an unqualified eye became clinically diagnosed with bacterial conjunctivitis, a conjunctival sample for bacterial culture and sensitivity was obtained from that eye on the day of diagnosis, and if applicable at the unqualified eye follow-up visit.

Clinical improvement of ocular signs and of ocular symptoms at day 6 was measured. Ocular signs of conjunctival hyperemia and mucopurulent discharge were measured in both eyes on a 4-point scale (0= none, 1= mild, 2= moderate, 3= severe) at each visit. Ocular symptoms of discomfort, including and tearing, were recorded using a 4-point scale (0= none, 1= mild, 2= moderate, 3= severe) at each visit.

Statistical and Analytical Plans

Table 5.3.1-4 Analysis Populations

Intent-to-Treat (ITT)	All randomized patients
Modified Intent-to-Treat (mITT) (Primary efficacy population)	All randomized patients who were culture positive at baseline
Per Protocol (PP)	All randomized patients who were culture positive at baseline, and had at least one follow-up visit and no major protocol deviations (Determined prior to database lock)
Safety	All randomized and treated patients

Patients may have had 1 or both eyes clinically diagnosed and treated at baseline. Those eyes are referred to as "qualified" eyes. One qualified eye for each patient was designated as the study eye according to the following algorithm:

- If both eyes were qualified, the eye with a positive bacterial conjunctivitis culture at baseline was designated as the study eye.
- If both qualified eyes were culture positive or both qualified eyes were culture negative at baseline, then the right eye was designated as the study eye.
- If only one eye was qualified, this eye was designated as the study eye.

Primary Efficacy Analysis

The primary statistical objective of the study was to demonstrate that gatifloxacin ophthalmic solution 0.5% is more effective than vehicle in the treatment of bacterial conjunctivitis.

The statistical null hypothesis was that there is no difference between gatifloxacin 0.5% and vehicle in clinical success rates. The alternative hypothesis is that there exists a difference. All statistical hypotheses were two-sided. A p-value $\leq$ 0.05 was considered statistically significant.

Secondary Efficacy Analysis
The clinical success rate was analyzed in the PP and ITT populations as secondary analyses using the same method as for the primary efficacy analysis.

Other secondary efficacy analyses were clinical success at the day 4 time point, microbiological cure, clinical improvement of ocular signs, and clinical improvement of ocular symptoms. The microbiological cure, ocular signs improvement, and ocular symptoms improvement analyses were done on data from the study eye in the mITT, PP, and ITT populations.

All secondary efficacy analyses were considered exploratory and no multiple adjustments were planned. All tests were two-sided and a p-value $\leq$ 0.05 was considered statistically significant.

Subgroup analyses of the clinical success rate, the primary efficacy variable, were performed by age group (i.e., 1 to 18, 19 to 65, and > 65 years of age) in the mITT population using Pearson's chi-square test or Fisher's exact test. Clinical success rate in the mITT population was summarized by investigator; no statistical testing was performed.

Microbiological Cure
Microbiological response was assessed for the study eye by comparing the bacterial count for each bacterial species at day 1 with the bacterial count for each corresponding bacterial species at the day 4 and day 6 time points. The microbial response was categorized as eradication, reduction, persistence or proliferation. A patient was considered to have microbiological cure if all bacterial species that had been present in the study eye at day 1 were eradicated. The microbiological cure rate was compared between the gatifloxacin and vehicle groups at the day 4 and day 6 time points using Pearson's chi-square test or Fisher's exact test.

In addition, the microbial response at the day 4 and day 6 time points was summarized by category (e.g., eradication, reduction), by bacterial classification (i.e., all organisms, all gram positive bacteria and all gram negative bacteria), and by each individual organism. No statistical testing was performed for these summaries.

Other Efficacy Analyses
Microbiological Sensitivity and Susceptibility
Sensitivity and susceptibility data were analyzed using the study eye in the mITT, PP, and ITT populations. Minimal inhibitory concentration (MIC) was determined for organisms above the threshold at a given visit. When multiple numbers of any one species were observed, MIC_{90} was calculated. Sensitivity [MIC (μg/mL)] was summarized using descriptive statistics by treatment group at each visit by bacterial classification and by individual organism. Statistical testing not performed.

The microbiological susceptibility and sensitivity data were analyzed using a study eye analysis at the day 1, 4, and 6 visits. The susceptibility analyses used the mITT and PP populations. The microbiological sensitivity analyses, as these analyses are intended to summarize organisms rather than patients. In addition, microbiological sensitivity was summarized by organism for the treated eye(s) in the ITT population.

Organisms above the pathological threshold for the qualified eye(s) at baseline (day 1) and also at the exit visit for patients in the mITT population were presented in frequency tables. No statistical testing was performed.

Safety Analysis
Data for adverse events, visual acuity, and biomicroscopy were analyzed using the safety population. Unless stated otherwise, for all analyses, Pearson's chi-square test or Fisher's exact test were used for the between-group comparisons. Adverse events and biomicroscopy findings were coded using MedDRA Version 10.0.

Protocol Deviations
Prior to database lock, the following important protocol deviations were excluded from the Per Protocol population:

- Study medication was administered after Day 5
- The exit visit (including eye culture) was not done within 12 to 48 hours after the last dose.
- Visit 2 (Day 4) occurred on Day 6
- A randomization error occurred.
- There was lack of compliance with study medication administration (e.g., medication was administered for < 5 days).
- Signs and/or symptoms were present for >96 hours prior to study entry.
- Patient did not meet entry criteria for severity of signs and/or symptoms.
- The method of counting fingers was used to assess visual acuity.
- The patient received prohibited concomitant medication.

Changes in the Conduct of the Study or Planned Analyses
The protocol was amended in December 2007. The amendment added collection of a conjunctival sample for adenovirus antigen in the unqualified eye if that eye became clinically diagnosed with bacterial conjunctivitis after day 1 but before day 6. It also added the following exclusion criterion:

> "Use of preserved topical ophthalmic medications/solutions within three hours prior to the first bacterial culture or the anticipated use of preserved topical ophthalmic medications/solutions during the study (except topical anesthetic used prior to the conjunctival sample tested for adenovirus antigen)."

The other changes in the amendment were made to ensure consistency between different sections of the protocol or were administrative in nature and did not affect the conduct of the study.

Changes to Analyses Following Database Lock
Treatment was to be administered for 5 days, with evaluation on day 6. To accommodate patient and physician schedules, this visit was permitted to occur on day 7, and may sometimes have occurred later. The visit window was defined as data collected on day 6 or later (the day 6 visit analysis). However, the typical self-limiting course of bacterial conjunctivitis could reduce observable differences between treatment groups for later time points. Therefore, sensitivity analyses that excluded data collected after day 6 (the up to day 6 analysis) were conducted. For the primary efficacy variable of clinical success, these analyses were conducted with and without LOCF imputation for the mITT and ITT populations. For all other efficacy variables, except bacterial susceptibility and sensitivity, an up to day 6 analysis was done (LOCF in the mITT and ITT populations).

Once it was determined that some patients who had been misrandomized received the wrong treatment, sensitivity analyses were conducted in which those patients were analyzed according to the treatment actually received (the treated analysis) in the mITT and ITT populations.

Sensitivity analyses were also performed with the worse eye. The definition for worse eye is compared to that of the study eye in the Table below. Day 6 visit and up to day 6 analyses were performed using worse eye (using LOCF for the mITT and ITT populations).

After the database was locked, in a communication dated 13 March 2009 that responded to the pre-NDA meeting package, FDA suggested that a summary table comparing clinical cure and microbiological eradication by pathogen would be useful, as would a by pathogen listing of clinical and microbiological efficacy outcomes and MIC values. Summary tables were prepared using both the day 6 visit and up to day 6 analysis methods. A listing was also created.

An additional change was that the category of all ocular adverse events was also summarized by treated and untreated eye. There were no other changes to the planned safety analyses.

Table 5.3.1– 5 Table of Investigators

10001	William F. Davitt III, MD (3809) Corona Research Consultants, Inc. 8815 Dyer St., Ste 165 El Paso, TX 79904	8	8
10002	Jesse M. De Leon, MD (3957) Center for Clinical Trials, LLC 16660 Paramount Blvd., Suite 301 Paramount, CA 90723	25	25
10006	Michael S. Korenfeld, MD (4666) Comprehensive Eye Care, Ltd. 901 East 3rd Street Washington, MO 63090	0	1
10007	Norman S. Levy, MD (0619) Florida Ophthalmic Institute 7106 NW 11th Place, Suite B Gainesville, FL 32605	3	2
10008	Daniel Long, MD (0356) Dr. Daniel A. Long – A Professional Medical Corporation 120 Meadowcrest St., #330 Gretna, LA 70056	24	26
10009	Dr. Douglas C. Lorenz, DO (3240) Nevada Eye & Ear 2598 Windmill Pkwy. Henderson, NV 89074	4	3
10010	Kenneth W. Olander, MD (1187) University Eye Surgeons 622 Smithview Drive Maryville, TN 37803	1	0
10011	Bernard R. Perez, MD (3858) International Eye Center 4506 Wishart Blvd. Tampa, FL 33603	10	11
10012	Howard I. Schenker, MD (2429) Rochester Ophthalmological Group, PC 2100 S. Clinton Ave. Rochester, NY 14618	7	8
10013	John D. Sheppard, MD (5082) Virginia Eye Consultants 241 Corporate Blvd. Norfolk, VA 23502	1	2
10014	Steve S. Spector, MD (3255) Presidential Eye Center, PA 1501 Presidential Way, Suite #11 West Palm Beach, FL 33401	2	2

10019	Yue-Kong Au, MD (10378) Yue-Kong Au MD, LLC 2539 Viking Drive, Suite 103 Bossier City, LA 71111	7	6
10021	Tomas Coronado, MD (10380) Sun Research Institute 303 E. Quincy St., Suite 101 San Antonio, TX 78215	5	4
10026	Warren H. Heller, MD (10382) Arizona Center for Clinical Trials, LLC 515 W. Buckeye Road, Suite 203 Phoenix, AZ 85003	24	26
10028	Paul A. Jorizzo, MD (10384) Medical Eye Center 2727 Barnett Road Medford, OR 97504	1	1
10029	Ranjan P. Malhotra, MD (10385) Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	14	14
10030	Eugene B. McLaurin, MD (10386) Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	10	9
10032	Stephen E. Smith, MD (10388) Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901	9	10
10034	William B. Trattler, MD (9750) Center for Excellence in Eye Care 8940 N. Kendall Drive, Suite 400-E Miami, FL 33176	0	2
10035	Francis J. Wapner, MD (10389) Advanced Eye Care 1250 East 3900 South, Suite 310 Salt Lake City, UT 84124	3	3
10036	Douglas G. Day, MD (2851) Omni Eye Services 5505 Peachtree-Dunwoody Road, Suite 300 Atlanta, GA 30342	1	0
10038	Michael E. Tepedino, MD (3212) Cornerstone Eye Care 307 Lindsay Street High Point, NC 27262	22	21
10042	Richard Sturm, MD (1587) Ophthalmic Consultants of Long Island 360 Merrick Road, 3rd Floor Lynbrook, NY 11563	1	1

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=287)	Vehicle (N=291)
10045	Henry Perry, MD (1777) Ophthalmic Consultants of Long Island Ryan Medical Arts Building 2000 North Village Avenue, Suite 402 Rockville Centre, NY 11570	2	2
10046	Stephen E. Pascucci, MD (3238) Eye Consultants of Bonita Springs, PLLC 23451 Walden Center Drive Bonita Springs, FL 34135	1	0
10048	Sherif M. El-Harazi, MD, MPH (10643) Lugene Eye Institute 801 S. Chevy Chase Drive, Suite 103 Glendale, CA 91205	6	6
10049	Jodi I. Luchs, MD (10647) South Shore Eye Care, LLP 2185 W. Wantagh Ave. Wantagh, NY 11793	3	2
10050	Barbara J. Arnold, MD, FACS (10650) Center for Clinical Trials of Sacramento, Inc. 7600 Hospital Drive Suite G Sacramento, CA 95823	9	9
10052	Bruce Kanengiser, MD (10660) Clinical Research Laboratories, Inc. 371 Hoes Lane, Suite 100 Piscataway, NJ 08854	4	5
10053	Lincoln Manzi, MD (10664) Southland Clinical Research Center 11100 Warner Avenue, Suites 214 and 352 Fountain Valley, CA 92708	2	2
10055	Shachar Tauber, MD (10704) St. John's Clinic – Eye Specialists 1229 East Seminole, Suite 430 Springfield, MO 65804	4	4
10058	Michael Howard Rotberg (2037) Charlotte Eye, Ear, Nose and Throat Associates, PA 6035 Fairview Road Charlotte, NC 28210	0	1
10059	Scott M. Corin, MD (11080) Advanced Eye Centers, Inc. 500 Faunce Corner, Road, Suite 110 Dartmouth, MA 02747	3	2
10061	James D. Branch, MD (3225) James D. Branch, MD 224 Town Run Lane Winston-Salem, NC 27101	2	2

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=287)	Vehicle (N=291)
10062	W. Colby Stewart, MD (11160) (Start date: 2008.05.13) Robert H. Stewart, MD (1458) (End date: 2008.05.13) Houston Eye Associates 2855 Gramercy St. Houston, TX 77025	0 4	0 4
10064	Jung Dao, MD (10290) Cornea Consultants of Arizona 3815 East Bell Road, Suite 2500 Phoenix, AZ 85032	4	5
10065	Mark Rubin, MD (2897) International Eye Associates 550 Memorial Circle, Suite N Ormond Beach, FL 32174	0	1
10066	Scott Portnoy, MD (11088) Allegheny Ophthalmology Associates 2853 Freeport Road Natrona Heights, PA 15065	2	2
10067	Phillip Lee Shettle, DO (11095) Shettle Eye Center 670 North Clearwater-Largo Road Largo, FL 33770	1	0
10071	Hope Yongsmith, MD (11188) Innovis Health 1702 South University Drive Fargo, ND 58103	2	2
10072	Jose Luis Perez-Becerra, MD (11183) Belle Vue Eye Centre 1327 SW Military Drive San Antonio, TX 78221	3	4
10073	Barry A. Bohn, MD (11314) Gulf Coast Research 314 Audubon Blvd. Lafayette, LA 70503	1	1
10074	Fred J. George, MD (11315) NEA Clinic Ophthalmology 416 East Washington Avenue, Suite B Jonesboro, AR 72401	1	2
10075	William Beck, MD (11318) Heartland Research Associates, LLC 700 Medical Center Drive, Suite 210 Newton, KS 67114	8	8
10076	Harold E. Reaves, MD (11322) Harold E. Reaves, MD Inc. 1127 Wilshire Blvd., Suite 504 Los Angeles, CA 90017	2	2

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=287)	Vehicle (N=291)
10077	Belu Allam, MD (11709) Northwood Pediatrics 25214 Borough Park Drive The Woodlands, TX 77380	4	4
10084	Kavita Surti, MD (10698) Atlantis Eye Care 236 West College Street Covina, CA 91723	20	16
10085	John Cowden, MD (1301) University of Missouri – Columbia M746 Health Sciences Center 1 Hospital Drive Columbia, MO 65212	1	0
10087	Jeffrey A. Hirschfield, MD (3727) SCORE Physician Alliance, LLC 6499 38th Avenue North, Suite A-2 Saint Petersburg, FL 33710	15	16
10090	Jeffrey M. Sage, DO (11712) Sage Eye Institute 1127 Wilshire Blvd., Suite 1600 Los Angeles, CA 90017	1	1
10094	Budrudin Kurwa, MD (12060) Kurwa Eye Center 301 W. Huntington Drive, Suite 107 Arcadia, CA 91007	0	1

Note: each investigator who was not an ophthalmologist had an ophthalmologist as a sub-investigator.

5.3.2 **Study 198782-005:** A 6 Day, Phase 3, Multicenter, Randomized, Double-masked, Parallel Study to Compare the Safety and Efficacy of Gatifloxacin 0.5% Ophthalmic Solution BID with that of Vehicle in the Treatment of Acute Bacterial Conjunctivitis

Table 5.3.2 Table of Investigators

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=430)	Vehicle (N=429)
10001	Marilou G. Cruz, MD (9727) Premier Health Research Center, LLC 11525 Brookshire Ave., Suite 400 Downey, CA 90241	16	16
10002	Cynthia Peralta, MD (9833) Doctors Medical Group 1300 S. Sunset Ave. West Covina, CA 91790	3	3
10003	David W. Cardona, MD (12209) Universal Biopharma Research Institute, Inc. Family Care Providers Medical Group 1300 North Fresno Street Fresno, CA 93703	1	0
10006	Robert M. Feldman, MD (2910) Robert Cizik Eye Clinic 6400 Fannin Street, Suite 1800 Houston, TX 77030	1	0
10007	Edgar Dapremont, Jr., MD (11131) Dapremont Eye Specialists 428 Courthouse Road Gulfport, MS 39507	8	8
10010	Gail Torkildsen, MD (4615) Andover Eye Associates 138 Haverhill Street Andover, MA 01810	1	0
10013	John D. Goosey, MD (12431) Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	12	13
10016	Brian K. Lepley, DO (12445) Brian K. Lepley, DO, MPH 809 SW 89th Street, Suite B Oklahoma City, OK 73139	1	1
10017	Victoria Sanchez-Bal, MD, FAAP (3769) Victoria Sanchez-Bal, MD, FAAP, Inc. 9540 E. Artesia Blvd., Suite 1 Bellflower, CA 90706	2	2

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=430)	Vehicle (N=429)
10020	David Kinsler, MD (10211) Vistar Eye Center 426 W. Main Street Salem, VA 24153	1	0
13001	Dr. Umang Mathur (11134) Dr. Shroff's Charity Eye Hospital 5027 Kedarnath Road Daryaganj, New Delhi – 110002	6	6
13002	Dr. Prashanth Garg (11166) L.V. Prasad Eye Institute Kallam Anji Reddy Campus L.V. Prasad Marg, Banjara Hills Hyderabad – 500 034	1	1
13003	Dr. Rohit Shetty (11175) Narayana Nethralaya Eye Hospital 121/c Chord Road, Rajajainagar 1st R Block Bangalore – 560010	2	0
13004	Dr. Rajesh Parekh (11110) Bhagwan mahaveer Jain Hospital Miller's Road Vasanthnagar Bangalore – 52	33	33
13006	Dr. Jeewan S. Titiyal (11106) Room no. 476, 4th floor Dr. R.P. Centre for Ophthalmic Sciences All India Institute of Medical Sciences Ansari Nagar (E) New Delhi – 110029	2	2
13007	Prof. Himadri Datta (11198) Regional Institute of Ophthalmology 88 College Street Calcutta – 700073	7	6
13008	Dr. Mrs. Yasmin Rusi Bhagat (11209) Head of Ophthalmology Department St. George's Hospital Fort, Mumbai – 400 001	41	42
13010	Dr. Kini Kulai Shobha (11215) Vasan Eyr Care Hospital F 22 Raman Road AVK Nagar, Salem – 4 Tamil Nadu	24	25
13011	Dr. Shilpa Kodkany (11133) Dr. Kodkany's Eye Centre Herwadkar Mansion, 1st Floor, Maruti Galli, Belgaum – 590 005 Karnataka	11	11

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=430)	Vehicle (N=429)
13012	Dr. Kala Baby Thottam (11216) Consultant Ophthalmologist, Cornea and Refractive Surgery Vasan Eye Care Hospital Opposite Shipyard, M.G. Road, Cochin – 682015	0	1
13013	Dr. Sundar Ram Shetty (11150) Globe Eye Foundation Eye Hospital A.I.R. Extension, NH-4, Hoskote, Bangalore – 562114	3	4
13014	Dr. Nita Shanbhag (11130) Omkar Eye Care Center 302/303 Koteshwar Plaza Junc of Jawaharlal Nehru Road and RHB Road Mulund (West) Mumbai – 400080	45	45
13015	Dr. Abraham Kurian (11120) Chaithanya Eye Hospital and Research Institute Kesavadasapuram, Trivandrum Kerala - 695004	4	5
13016	Dr. Ganesh Balasubramaniam (11589) Jaya Eye Care Centre 12, Norton 3rd Lane Mandavelipakkam, Chennai – 600028	12	12
13017	Dr. Jyoti Shetty (11590) B W Lion's Superspecialty Eye Hospital 5, Lion's Eye Hospital Road, Off JC Road, Bangalore – 560 002	6	7
13018	Dr. Nelson Jesudasan C.A. (11591) Institute of Ophthalmology Joseph Eye Hospital Melaputhur Trichy – 620001	33	32
13019	Dr. Vinay R. Murthy (11592) Prabha Eye Clinic and Research Center No. 504, 40th Cross, 8th Block, Jayanagar, Bangalore – 70	19	18
13020	Dr. Shanta A. Motwane (11593) KJ Somaiya Medical College & Hospital Near Everord Nagar, Sion, Mumbai – 400 022	36	36

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=430)	Vehicle (N=429)
13021	Dr. G. Kummararaj (11607) Dr. A. Govindarajan Eye Hospitals No. 6, Officers Colony, Puthur, Tiruchirappalli – 620017 Tamil Nadu, India	44	43
13023	Prof. K. Vasantha (11595) Corneal Department, Regional Institute of Ophthalmology Rukmani Lakshmipati Road, Egmore, Chennai – 600008	10	10
13024	Dr. Sanita Mary George Korah (11596) Ophthalmology Department Christian Medical College Arni Road Vellore – 632004	3	3
13025	Dr. Suvira Jain (11597) K.B. Haji Bachooali Eye Hospital Jehangir Merwanji Street Parel, Mumbai – 12	5	5
13026	Dr. K. Satish (11598) K.R. Hospital Mysore 560001 Karnataka	2	2
13027	Dr. Meenakshi Yadav Dhar (11600) Amrita Institute of Medial Sciences and Research Center Amrita Lane, Elamakkara Post Kochi, Kerala – 682026	5	5
13028	Dr. Vishwanathan (11602) Sri Ramachandra Medical College and Research Institute Porur, Chennai – 600 116 Tamil Nadu	3	3
13029	Dr. Leslie Ravi Kumar (11603) Medisys Clinisearch Bangalore Eye Hospital and Retina Center #426, 4th Cross, 2nd Block Kalyan Nagar Bangalore – 560043	18	20
13030	Dr. Shreesh Kumar (11604) The Eye Foundation D.B. Road, R S Puram Coimbatore – 641002 Tamil Nadu	4	3
13031	Dr. Anish M. R. (4/16/2008-) (11605) Dr. Y. Umesh (10/10/2007 – 4/16/2008) Sankara Eye Centre Sathy Road Shivanandapuram Coimbatote – 641035	4	4

Site No.	Principal Investigator Name and Address	Gatifloxacin 0.5% (N=430)	Vehicle (N=429)
13032	Dr. Sujatha Mohan (11606) Rajan Eye Care Hospital 5, Vidyodaya East 2nd Street, T. Nagar, Chennai – 600 018	1	2

Note: each investigator who was not an ophthalmologist had an ophthalmologist as a sub-investigator.

6 Review of Efficacy

6.1 Efficacy Summary – Study 198782-004

Study 198782-004 was submitted in support of the proposed indication, the treatment of bacterial conjunctivitis in patients one year or older.

6.1.1 Methods

Clinical study reports, clinical protocols and literature references were submitted related to the two clinical trials submitted in support of the New Drug Application.

6.1.2 Demographics

Table 6.1.2-1 Demographic Data (ITT Population [b])

	Gatifloxacin 0.5% N=287	Vehicle N=291	p-value [a]
Age (years)			0.946
Mean	30.7	30.6	
SD	25.4	24.4	
Range	1-89	1-92	
Sex, N (%)			0.464
Male	126 (43.9%)	119 (40.9%)	
Female	161 (56.1%)	172 (59.1%)	
Race, N (%)			0.746
Caucasian	150 (52.3)	156 (53.6)	
Non-Caucasian	137 (47.7)	135 (46.4)	

a P-value for age from 1-way analysis of variance, and for sex and race from Pearson's chi-square test or Fisher's exact test. **b** All randomized patients

Table 6.1.2-2 Demographic Data (mITT Population [c])

	Gatifloxacin 0.5% N=167	Vehicle N=158	p-value
Age (years)			0.148 [a]
Mean	30.7	26.4	
SD	28.7	24.5	
Range	1-89	1-88	
No. Enrolled			
≥ 18 years	88	76	0.096
16-17 years	3	4	0.721
11-15 years	8	14	0.824
6-10 years	23	25	0.436
1-5 years	45	39	0.925
Sex, N (%)			0.605 [b]
Male	83 (49.7%)	74 (46.8%)	
Female	84 (50.3%)	84 (53.2%)	
Race, N (%)			0.605 [b]
Caucasian	84 (50.3)	84 (53.2)	
Non-Caucasian	83 (49.7)	74 (46.8)	

a One way analysis of variance **b** Pearson's chi-square test **c** Primary efficacy analysis population all randomized subjects who are culture positive at baseline

Reviewer's Comment:
There were no significant differences in the treatment groups at baseline with regard to age or sex in either the ITT or mITT populations.

6.1.3 Subject Disposition

A total of 578 patients were enrolled and 552 patients (95.5%) completed the study. There were 67 patients who were screening failures. The most frequent reason for study ineligibility was a positive adenovirus test (33 patients).

Table 6.1.3-1 Analysis Populations

	Gatifloxacin 0.5%	Vehicle
ITT Population [a]	287	291
mITT Population [a]	167	158
PP Population	142	138
Safety Population [a]	288	289

a Used for efficacy analyses

Table 6.1.3-2 Disposition of Subjects Randomized to Treatment (ITT Population)

	Gatifloxacin 0.5%	Vehicle	Total
ITT Population	**287**	**291**	**578**
Completed, N (%)	276 (96.2)	276 (94.8)	552 (95.5)
Discontinued, N (%)	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
Lack of efficacy	2 (0.7)	2 (0.7)	4 (0.7)
Lost to follow-up	3 (1.0)	0	3 (0.5)
Personal reasons	0	3 (1.0)	3 (0.5)
Protocol violation	1 (0.3)	0	1 (0.2)
Other [a]	3 (1.0)	5 (1.7)	8 (1.4)

a Other reasons included schedule conflict with investigator (n = 1) and withdrew consent (n = 2) for the gatifloxacin group and screen failure with lens-related keratoconjunctivitis inadvertently randomized (n = 1), lack of efficacy reported by patient (n = 2), withdrew consent (n = 1), and non-compliance (n = 1) for vehicle group.

Reviewer's Comment:
There were slightly more subject discontinuations in the vehicle treatment group. The difference was not statistically significant.

Table 6.1.3-3 Disposition of Subjects Randomized to Treatment (mITT[a] Population)

	Gatifloxacin 0.5%	Vehicle	Total
mITT Population	**167**	**158**	**325**
Completed, N (%)	161 (96.4)	152 (96.2)	313 (96.3)
Discontinued, N (%)	6 (3.6)	6 (3.8)	12 (3.7)
Adverse Events	2 (1.2)	3 (1.9)	5 (1.5)
-Ocular	2 (1.2)	3 (1.9)	5 (1.5)
-Non-ocular	0	0	0
Lack of efficacy	0	1 (0.6)	1 (0.3)
Lost to follow-up	0	0	0
Personal reasons	0	1 (0.6)	1 (0.3)
Protocol violation	1 (0.6)	0	1 (0.3)
Other	3 (18)	1 (0.6)	4 (1.2)

a Includes all randomized subjects who are culture positive at baseline.

Reviewer's Comment:
There was no treatment group difference in discontinuations in the modified Intent-to-Treat population.

Table 6.1.3-4 Subjects Discontinued from Treatment or Study ITT Population

Reason for Discontinuation	Treatment	Center Number	Patient Number
Adverse event – worsening of bacterial conjunctivitis	Gatifloxacin 0.5%	10011	1514
Adverse event – worsening of bacterial conjunctivitis	Gatifloxacin 0.5%	10076	1617 [a]
Adverse event – worsening of bacterial conjunctivitis	Vehicle	10002	1310
Adverse event – worsening of bacterial conjunctivitis	Vehicle	10009	1097
Adverse event – Episcleritis	Vehicle	10012	1089
Adverse event – Dacryocystitis	Vehicle	10029	1508
Adverse event – Hyperopic shift	Vehicle	10048	1210
Adverse event – Periorbital cellulitis	Vehicle	10084	1314 [a]
Lack of Efficacy	Gatifloxacin 0.5%	10038	1523
Lack of Efficacy	Gatifloxacin 0.5%	10049	1495
Lack of Efficacy [b]	Vehicle	10001	1018
Lack of Efficacy	Vehicle	10011	1061
Lack of Efficacy	Vehicle	10034	1263
Lack of Efficacy [b]	Vehicle	10059	1138
Lost to Follow-up	Gatifloxacin 0.5%	10021	1075
Lost to Follow-up	Gatifloxacin 0.5%	10026	1144
Lost to Follow-up	Gatifloxacin 0.5%	10077	1435
Non-compliance	Vehicle	10001	1379
Other – Day 6 visit outside of window because PI not available	Gatifloxacin 0.5%	10050	1469
Personal reasons	Vehicle	10026	1482
Personal reasons	Vehicle	10029	1232
Personal reasons	Vehicle	10084	1585
Protocol violation – Baseline visual acuity - CF	Gatifloxacin 0.5%	10048	1205
Screening failure – CLs related keratoconjunctitivits	Vehicle	10084	1336
Withdrew consent	Gatifloxacin 0.5%	10002	1221
Withdrew consent	Gatifloxacin 0.5%	10002	1236
Withdrew consent [c]	Vehicle	10012	1340

a Both of patient's eyes were study eyes and experienced the adverse event. Both eyes were removed from treatment due to AE. **b** As determined by the subject **c** Consent withdrawn by parent for uncooperative child.

Reviewer's Comment:
Discontinuations due to adverse events, lack of efficacy and personal reasons were more frequent in the vehicle group.

Table 6.1.3-5 Randomized Subjects with Major Protocol Deviations Excluded from the Per Protocol Population

Protocol violation	Treatment Group	Center Number	Patient Number
Other antibiotic use	Gatifloxacin 0.5%	10001	1136
Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10001	1392
Dosed beyond Day 5	Gatifloxacin 0.5%	10007	1430
Dosed beyond day 5	Gatifloxacin 0.5%	10007	1450
Dosed < 4 hrs before Day 4 visit	Gatifloxacin 0.5%	10008	1187
Dosed beyond Day 5 Dosed with Lumigan, Alphagan continuously	Gatifloxacin 0.5%	10009	1044
Incorrect study drug kit used Oral antibiotic use Dosed < 12 hrs before Day 6 visit	Gatifloxacin 0.5%	10009	1632
Dosed beyond Day 5	Gatifloxacin 0.5%	10011	1055
Dosed beyond Day 5 Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10012	1070
Lost study drug kit. Would not return for replacement	Gatifloxacin 0.5%	10014	1384
Dosed beyond Day 5	Gatifloxacin 0.5%	10014	1590
Day 6 visit occurred on Day 8	Gatifloxacin 0.5%	10021	1011
Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10021	1458
Dosed beyond Day 5 Day 6 visit occurred on Day 8	Gatifloxacin 0.5%	10021	1586
Day 5 doses missed. Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10026	1437
Day 6 visit occurred on Day 8 Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10028	1137
Inclusion / Exclusion Criteria not met	Gatifloxacin 0.5%	10030	1639
Dosed beyond Day 5	Gatifloxacin 0.5%	10032	1156
Dosed beyond Day 5 Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10035	1092
Randomization without IVRS - Incorrect study drug kit	Gatifloxacin 0.5%	10036	1219
Dosed beyond Day 5	Gatifloxacin 0.5%	10038	1202
Dosed beyond Day 5	Gatifloxacin 0.5%	10038	1354
Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10038	1412

Protocol violation	Treatment Group	Center Number	Patient Number
Dosed beyond Day 5	Gatifloxacin 0.5%	10042	1223
Dosed beyond Day 5.	Gatifloxacin 0.5%	10045	1542
Randomization without IVRS - Incorrect study drug kit Day 4 and 6 visits outside of windows	Gatifloxacin 0.5%	10046	1575
Inclusion Criteria – visual acuity CF	Gatifloxacin 0.5%	10048	1205
Dosed beyond Day 5	Gatifloxacin 0.5%	10049	1358
Exclusion Criteria – Symptoms 1 week prior to enrollment	Gatifloxacin 0.5%	10050	1447
Dosed 4 days only Day 6 visit occurred on Day 5	Gatifloxacin 0.5%	10050	1469
Dosed beyond Day 5	Gatifloxacin 0.5%	10050	1624
Dosed beyond Day 5 Day 4 visit occurred on Day 6 Cosopt taken throughout	Gatifloxacin 0.5%	10061	1304
Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10066	1548
Randomization without IVRS - Incorrect study drug kit	Gatifloxacin 0.5%	10071	1233
Baseline microbial culture misplaced then sent in >7 days later	Gatifloxacin 0.5%	10075	1327
Fluorescein used before collecting microbial culture Dosed < 12 hours before Day 6 visit	Gatifloxacin 0.5%	10075	1410
Dosed on Day 6	Gatifloxacin 0.5%	10075	1432
Dosed < 12 hours before Day 6 visit	Gatifloxacin 0.5%	10076	1617
Dosed on Day 6	Gatifloxacin 0.5%	10084	1224
Dosed < 12 hours before Day 6 visit	Gatifloxacin 0.5%	10084	1315
Dosed < 12 hours before Day 6 visit	Gatifloxacin 0.5%	10084	1331
Dosed beyond Day 6 Day 6 visit outside window	Gatifloxacin 0.5%	10084	1361
Visit 2 occurred on Day 6	Gatifloxacin 0.5%	10084	1378
Missed doses on Day 4 and Day 5 Visit 3 on Day 5, 12 hrs after last dose	Gatifloxacin 0.5%	10084	1415
Exit visit occurred > 48 hrs after last dose	Gatifloxacin 0.5%	10084	1552
Visit 2 occurred on Day 3 Day 6 visit occurred on Day 9	Gatifloxacin 0.5%	10084	1607
Dosed beyond Day 6 Visit 3 occurred on Day 8, outside of window	Gatifloxacin 0.5%	10084	1627
Day 6 visit was > 48 hrs after last dose	Vehicle	10001	1090
Day 6 visit was > 48 hrs after last dose	Vehicle	10001	1317
Non-compliant with dosing	Vehicle	10001	1379
Exclusion Criteria – Symptoms > 96 hrs prior to enrollment	Vehicle	10006	1357
Dosed beyond Day 5	Vehicle	10007	1022
Dosed beyond Day 5	Vehicle	10011	1029
Incorrect dosing Days 3 and 4	Vehicle	10011	1059
Visit 3 occurred on Day 10	Vehicle	10011	1345

Protocol violation	Treatment Group	Center Number	Patient Number
Dosed beyond Day 5	Vehicle	10014	1244
Day 6 visit was > 48 hrs after last dose	Vehicle	10021	1459
Day 6 visit was > 48 hrs after last dose	Vehicle	10026	1226
Dosed beyond Day 5 Exit visit/ Day 6 visit occurred on Day 8 within 12 – 48 hrs of last dose	Vehicle	10026	1436
Inclusion Criteria – Did not have 2+ hyperemia at baseline	Vehicle	10029	1232
Dosed beyond Day 5	Vehicle	10032	1157
Visit 3 > 48 hours after last dose	Vehicle	10032	1185
Inclusion Criteria – Did not have 2+ hyperemia at baseline	Vehicle	10034	1263
Exclusion Criteria – Symptoms > 96 hrs prior to enrollment Dosed with prednisone throughout study Kit dispensed without IVRS Dosed beyond Day 5 Day 6 visit was > 48 hrs after last dose	Vehicle	10034	1319
Dosed beyond Day 5	Vehicle	10038	1369
Dosed beyond Day 5 Day 6 visit occurred within 12 – 48 hrs of last dose	Vehicle	10048	1554
Day 6 visit occurred outside of window Last dose on Day 4	Vehicle	10050	1362
Day 4 visit occurred outside of window	Vehicle	10055	1289
Dosed with systemic corticosteroid during study Day 6 visit was > 48 hrs after last dose	Vehicle	10055	1609
Dosed beyond Day 5	Vehicle	10058	1095
Incorrect study kit dispensed	Vehicle	10061	1568
Dilating drops prior to microbial collection	Vehicle	10065	1448
Day 6 visit occurred outside of window	Vehicle	10071	1241
Inclusion Criteria – Did not have 1+ discharge at baseline	Vehicle	10075	1284
Dosed beyond Day 5	Vehicle	10075	1308
Incorrect study kit dispensed	Vehicle	10075	1338
Discontinued dosing on Day 4	Vehicle	10084	1314
Day 6 visit was > 48 hrs after last dose	Vehicle	10084	1399
Day 4 visit occurred on Day 6	Vehicle	10084	1467
Day 4 visit occurred on Day 6 Day 6 visit occurred on Day 8, > 48 hrs after last dose	Vehicle	10084	1518
Day 4 visit occurred on Day 6 Day 6 visit occurred on Day 8	Vehicle	10084	1519
Day 6 visit was > 48 hrs after last dose	Vehicle	10084	1551

Protocol violation	Treatment Group	Center Number	Patient Number
Day 4 visit occurred on Day 6 Day 6 visit occurred on Day 8, > 48 hrs after last dose	Vehicle	10084	1618
Dosed beyond Day 5	Vehicle	10090	1531

Reviewer's Comment:
Seven patients did not receive the medication kit to which they were randomized. Patient (10009-1632) was randomized to gatifloxacin but received vehicle. Patients (10034-1319 and 10075-1338) were randomized to vehicle but received gatifloxacin. These subjects were included in the mITT population. For all planned efficacy analyses these patients were included in the group to which they were randomized.

6.1.4 Analysis of Primary Endpoint(s)

Table 6.1.4 Primary Efficacy Analysis
Clinical Success in the Study Eye
mITT (LOCF) Population

	Day 6 Visit Analysis (Primary Analysis Method)		
Population (Analysis) Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
mITT (LOCF)			
Day 4 n/N (%)	56/167 (33.5)	33/158 (20.9)	0.011
Day 6 n/N (%)	**125/167 (74.9)**	**103/158 (65.2)**	**0.057**

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, the Fisher's exact test was used.

Reviewer's Comment:
The proportion of patients who achieved clinical success in the modified Intent-to-Treat population was numerically greater in the gatifloxacin group compared to the vehicle group; it reaches marginal statistical significance in the Day 6 Visit analysis.

6.1.5 Analysis of Secondary Endpoints(s)

Microbiological Cure
The planned secondary efficacy endpoints were microbiological cure and clinical improvement. A conjunctival sample for bacterial culture and sensitivity was obtained from the qualified eye(s) at each visit, and was used to determine microbiological cure and microbiological response. A

patient was considered to have microbiological cure if all bacterial species present at day 1 (baseline) were eradicated.

Table 6.1.5-1 Microbiological Cure in the Study Eye
mITT Population

	Day 6 Visit Analysis (Primary Analysis Method)		
Visit / Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
Day 4 n/N (%)	145/167 (86.8)	81/158 (51.3)	< 0.001
Day 6 n/N (%)	149/167 (89.2)	97/158 (61.4)	< 0.001

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, the Fisher's exact test was used.

Reviewer's Comment:
The proportion of patients who achieved microbiological cure in the modified Intent-to-Treat population was numerically greater in the gatifloxacin group compared to the vehicle group. This difference was statistically significant as well.

Table 6.1.5-2
Microbiological Eradication in the Study Eye by
Most Frequent Organisms at the Day 6 Time Point
mITT Population

	Day 6 Visit Analysis (Primary Analysis Method)			
Organism	**Gatifloxacin (N=167)**		**Vehicle (N=158)**	
	No. of infections	**No. of eradications (%)**	**# of infections**	**# of eradications**
Haemophilus influenzae	62	60 (96.8%)	46	26 (56.5%)
Streptococcus pneumoniae	40	35 (87.5%)	40	25 (62.5%)
Staphylococcus aureus	23	20 (87.0%)	18	13 (72.2%)
Staphylococcus epidermidis	20	16 (80.0%)	25	17 (68.0%)
Streptococcus mitis group	10	10 (100.0%)	6	6 (100.0%)
Streptococcus oralis	7	7 (100.0%)	4	4 (100.0%)

Reviewer's Comment:
The percentage of microbiological eradications was greater in the gatifloxacin group than in the vehicle group for Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus, and Staphylococcus epidermidis.

6.1.6 Other Endpoints

No additional endpoints were required to establish the efficacy of the drug product.

6.1.7 Subpopulations

Table 6.1.7-5 Clinical Success in the Study Eye - Day 6 Analysis [a]
mITT population (LOCF)

	Day 6 Visit Analysis		
Age Group Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
1 – 5 years			
Day 4 n/N (%)	17/45 (37.8)	8/39 (20.5)	
Day 6 n/N (%)	39/45 (86.7)	23/39 (59.0)	0.004
6 – 10 years			
Day 4 n/N (%)	6/23 (26.1)	7/25 (28.0)	
Day 6 n/N (%)	20/23 (87.0)	19/25 (76.0)	0.466 [b]
11 – 15 years			
Day 4 n/N (%)	4/8 (50.0)	3/14 (21.4)	
Day 6 n/N (%)	7/8 (87.5)	11/14 (78.6)	> 0.999 [b]
16 – 17 years			
Day 4 n/N (%)	1/3 (33.3)	0/4 (00.0)	
Day 6 n/N (%)	2/3 (66.7)	2/4 (50.0)	> 0.999 [b]
1 – 17 years			
Day 4 n/N (%)	28/79 (35.4)(33.3)	18/82 (22.0)	0.058
Day 6 n/N (%)	**68/79 (86.1)**	**55/82 (67.1)**	**0.005**

a Day 6 is the primary time point for the assessment of clinical success.
b P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, then Fisher's exact test was used.

Reviewer's Comment:
For the overall pediatric population, patients age 1 – 17 years, the treatment group difference in the proportion of patients who achieved clinical success in the mITT population was statistically significant in favor of the gatifloxacin group at Day 6 (Day 6 visit analysis).

The treatment group difference in the proportion of patients who achieved clinical success in the modified Intent-to-Treat population was statistically significant in favor of the gatifloxacin group at Day 6 (Day 6 visit analysis) for patients age 1- 5 years.

The treatment group differences did not reach statistical significance for the 6 -10 year, 11-15 year or 16-17 year age groups. Comparisons in these age groups were underpowered.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The concentration of 0.5% gatifloxacin was chosen for Zymaxid based on the efficacy and safety of Zymar. The formulation was modified by an increase in the drug substance concentration, decreases in pH to ensure drug solubility and in the sodium chloride concentration for tonicity.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In both phase 3 trials, patients were evaluated at a test-of-cure visit approximately 60-90 hours following the last dose. No evidence of tolerance or withdrawal effects was detected.

6.1.10 Additional Efficacy Issues/Analyses

The results of an alternative analysis, the Up to Day 6 Analysis which excluded exit visit data collected after Day 6 is presented here.

Table 6.1.10-1 Clinical Success in the Study Eye
Up to Day 6 Analysis [a]

	Up to Day 6 Visit Analysis		
Population (Analysis) Time point	**Gatifloxacin**	**Vehicle**	**p value [b]**
mITT (LOCF)			
Day 4 n/N (%)	56/167 (33.5)	33/158 (20.9)	0.011
Day 6 n/N (%)	**107/167 (64.1)**	**79/158 (50.0)**	**0.010**
PP			
Day 4 n/N (%)	48/137 (35.0)	32/135 (23.7)	0.040
Day 6 n/N (%)	80/102 (78.4)	67/94 (71.3)	0.248
ITT (LOCF)			
Day 4 n/N (%)	105/287 (36.6)	88/291 (30.2)	0.106
Day 6 n/N (%)	190/287 (66.2)	160/291 (55.0)	0.006

a Includes all data collected up to and including Day 6 but excluding data collected after Day 6.

Reviewer's Comment:
The treatment group difference in the proportion of patients who achieved clinical success in the modified Intent-to-Treat population was statistically significant in favor of the gatifloxacin group at Day 4 and Day 6 in the Up to Day 6 analysis.

Table 6.1.10-2 Clinical Success and Microbiological Cure by Organism in the Study Eye at the Day 6 Time Point (mITT Population)

Organism	Day 6 Visit Analysis				Up to Day 6 Visit Analysis			
	Gatifloxacin n/N (%)		Vehicle n/N (%)		Gatifloxacin n/N (%)		Vehicle n/N (%)	
	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure
Haemophilus influenzae	40/42 (95.2)	42/42 (100)	23/40 (57.5)	21/40 (52.5)	37/42 (88.1)	41/42 (97.6)	16/40 (40.0)	21/40 (52.5)
Staphylococcus aureus	11/20 (55.0)	15/20 (75.0)	9/13 (69.2)	8/13 (61.5)	10/10 (50.0)	15/20 (75.0)	5/13 (38.5)	6/13 (46.2)
Staphylococcus epidermidis	6/7 (85.7)	5/7 (71.4)	8/9 (88.9)	5/9 (55.6)	6/7 (85.7)	5/7 (71.4)	6/9 (66.7)	5/9 (55.6)
Streptococcus pneumoniae	27/32 (84.4)	28/32 (87.5)	26/37 (70.3)	22/37 (59.5)	19/32 (59.4)	29/32 (90.6)	21/37 (56.8)	24/37 (64.9)
Streptococcus mitis group	0/2 (0.0)	2/2 (100)	4/5 (80.0)	5/5 (100)	0/2 (0.0)	2/2 (100)	4/5 (80.0)	5/5 (100)
Streptococcus oralis	1/2 (50.0)	1/2 (50.0)	1/3 (33.3)	3/3 (100)	1/2 (50.0)	1/2 (50.0)	1/3 (33.3)	3/3 (100)
Mixed infection total [a]	31/44 (70.5)	39/44 (88.6)	27/36 (75.0)	22/36 (61.1)	27/44 (61.4)	39/44 (88.6)	21/36 (58.3)	19/36 (52.8)

N= number of patients with that organism present above threshold in the study eye at baseline
a Patients with mixed infection are not included in rows for individual organisms.

Reviewer's Comment:
There were ≥ 10 isolates with at least a 50% clinical success rate of Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, and Haemophilus influenzae.

Table 6.1.10-3
Clinical Success and Microbiological Cure [a] in the Study Eye
by Organism at the Day 6 Time Point
(Pooled mITT Population, LOCF)

Organism	Up to Day 6 Visit Analysis			
	Gatifloxacin n/N (%)		Vehicle n/N (%)	
	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure
Gram Positive bacilli isolated [b]	2/5 (40.0)	5/5 (100)	0/0 (0.0)	0/0 (0.0)
Gram positive cocci in clusters [b]	6/12 (50.0)	7/12 (58.3)	10/22 (45.5)	12/22 (54.5)
Haemophilus influenzae	38/43 (88.4)	42/43 (97.7)	19/45 (42.2)	26/45 (57.8)
(b) (4)				
Pseudomonas aeruginosa	2/7 (28.6)	6/7 (85.7)	4/10 (40.0)	9/10 (90.0)
Staphylococcus aureus	26/52 (50.0)	45/52 (86.5)	13/37 (35.1)	22/37 (59.5)
Staphylococcus epidermidis	21/35 (60.0)	31/35 (88.6)	14/27 (51.9)	22/27 (81.5)
(b) (4)				
Staphylococcus hominis	3/7 (42.9)	7/7 (100)	7/15 (46.7)	15/15 (100)
Staphylococcus warneri	5/11 (45.5)	10/11 (90.9)	1/2 (50.0)	2/2 (100)
(b) (4)				
Streptococcus oralis	2/5 (40.0)	4/5 (80.0)	1/4 (25.0)	4/4 (100)
Streptococcus pneumoniae	21/34 (61.8)	30/34 (88.2)	22/38 (57.9)	24/38 (63.2)

Organisms were included if there were ≥ 5 patients in the gatifloxacin group with only that organism present above threshold at baseline and an evaluable result at the day 6 time point.
N= number of patients with that organism present above threshold in the study eye at baseline and an evaluable response at the day 6 time point
Patients with mixed infection are not included.
a Microbiological cure = all bacterial species present above threshold in the study eye at baseline were eradicated.
b These organisms were not identified to the genus and species level.

Reviewer's Comments:

Efficacy defined as clinical success based on the number of isolates seen, e.g. 5-9 isolates with ≥ 80% clinical success or ≥10 isolates with ≥ 50% clinical success, was demonstrated in patients with cultures positive for these known ophthalmic pathogens: Staphylococcus aureus,

Staphylococcus epidermidis, [redacted](b) (4), *Streptococcus pneumoniae, and Haemophilus influenzae.*

The applicant proposed inclusion of [redacted](b) (4) *in the product label. However, since no isolates of these ocular pathogens were cultured from the gatifloxacin-treated patients in the U.S. study, they should not be included in the product label.*

Table 6.1.10-4
Clinical Success and Microbiological Cure [a] in the Study Eye at the Day 6 Time Point by Organism in Selected Mixed Infections (Pooled mITT Population, LOCF)

Organism	Up to Day 6 Visit Analysis			
	Gatifloxacin n/N (%)		Vehicle n/N (%)	
	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure
Streptococcus mitis group	8/9 (88.9)	9/9 (100)	3/4 (75.0)	3/4 (75.0)
Streptococcus oralis	5/7 (71.4)	6/7 (85.7)	1/2 (50.0)	1/2 (50.0)

Includes organisms that were identified in ≤ 5 single organism infections in the gatifloxacin group and ≥ 5 mixed infections in the gatifloxacin group.
N= number of patients with that organism present above threshold in the study eye at baseline and an evaluable response at the day 6 time point
Microbiological cure = all bacterial species present above threshold in the study eye at baseline were eradicated.

Reviewer's Comments:

When organisms that were identified in ≤ 5 single organism infections in the gatifloxacin group and ≥ 5 mixed infections in the gatifloxacin group are combined, Streptococcus mitis group and Streptococcus oralis meet the efficacy requirement defined as clinical success based on the number of isolates seen, e.g. 5-9 isolates with ≥ 80% clinical success or ≥10 isolates with ≥ 50% clinical success.

Thus, efficacy was demonstrated in patients with cultures positive for:

> *Gram-positive microorganisms: Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis group*, Streptococcus oralis*, and Streptococcus pneumoniae.*
>
> *Aerobic and facultative Gram-negative microorganisms: Haemophilus influenzae.*
>
> **Efficacy of this organism was studied in fewer than 10 infections.*

6.2 Efficacy Summary – Study 198782-005

Study 198782-005 was submitted in support of the proposed indication, the treatment of bacterial conjunctivitis in patients one year or older.

Reviewer's Comment:
Significant data integrity issues were found at Site 13020 which enrolled 72 patients of whom 31 were included in the mITT population. All efficacy analyses were performed excluding Site 13020 due to the data integrity issues identified by the sponsor.

Further details on the nature of the data integrity issue identified are presented in Section 3.2.

6.2.1 Methods

Clinical study reports, clinical protocols and literature references were submitted related to the two clinical trials submitted in support of the New Drug Application.

6.2.2 Demographics

Table 6.2.2-1 Demographic Data
(ITT Population Without Site 13020)

	Gatifloxacin 0.5% N=394	Vehicle N=393	p-value
Age (years)			0.141 [a]
Mean	38.8	36.7	
SD	19.9	19.7	
Range	1-86	1-87	
Sex, N (%)			0.063 [b]
Male	221 (56.1%)	246 (62.6%)	
Female	173 (43.9%)	147 (37.4%)	
Race, N (%)			0.461 [b]
Caucasian	17 (4.3%)	13 (3.3%)	
Non-Caucasian	377 (95.7%)	380 (96.7%)	

a One way analysis of variance **b** Pearson's chi-square or Fisher's exact test

**Table 6.2.2-2 Demographic Data
(mITT Population Without Site 13020)**

	Gatifloxacin 0.5% N=166	Vehicle N=167	p-value [a]
Age (years)			0.943
Mean	38.9	38.8	
SD	20.4	20.4	
Range	1-86	1-87	
Sex, N (%)			0.206
Male	88 (53.0%)	100 (59.9%)	
Female	78 (47.0%)	67 (40.1%)	
Race, N (%)			0.994
Caucasian	3 (1.8)	3 (1.8)	
Non-Caucasian	163 (98.2)	164 (98.2)	

a P-value for age from 1-way analysis of variance, and for sex and race from Pearson's chi-square test.

Reviewer's Comment:
Significant data integrity issues were found at Site 13020 which enrolled 72 patients of whom 31 were included in the mITT population.

The Demographic data are presented without Site 13020 above and including Site 13020 below. There were no significant treatment group differences in Demographic data in either the ITT or mITT populations whether Site 13020 is included or excluded.

6.2.3 Subject Disposition

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.

Table 6.2.3 -1 Analysis Populations

	All Sites		Site 13020 Excluded	
Population	Gatifloxacin 0.5%	Vehicle	Gatifloxacin 0.5%	Vehicle
ITT	430 [a]	429 [a]	394	393
mITT	179	185	166 [b]	167 [b]
PP	173	174	160	156
Safety	429	427	N/A	N/A

a All sites were included in safety analyses.
b The mITT population excluding Site 13020 was considered primary for efficacy analyses.

Table 6.2.3 -2 Disposition of Subjects
(ITT Population Without Site 13020)

	Gatifloxacin 0.5%	Vehicle	Total
ITT Population	**394**	**393**	**797**
Completed, N (%)	366 (92.9)	363 (92.4)	729 (92.6)
Discontinued, N (%)	28 (7.1)	30 (7.6)	58 (7.4)
Adverse Events	6 (1.5)	4(1.0)	10 (1.3)
-Ocular	4 (1.0)	3 (0.8)	7 (0.9)
-Non-ocular	2 (0.5)	1 (0.3)	3 (0.4)
Lack of efficacy	0	0	0
Pregnancy	0	0	0
Lost to follow-up	18 (4.6)	20 (5.1)	38 (4.8)
Personal reasons	2 (0.5)	2 (0.5)	4 (0.5)
Protocol violation	1 (0.3)	0	1 (0.1)
Other [a]	1 (0.3)	4 (1.0)	5 (0.6)

a Includes all randomized patients

Table 6.2.3 -3 Disposition of Subjects
(mITT Population Without Site 13020)

	Gatifloxacin 0.5%	Vehicle	Total
mITT Population	**166**	**167**	**333**
Completed, N (%)	162 (97.6)	157 (94.0)	319 (95.9)
Discontinued, N (%)	4 (2.4)	10 (6.0)	14 (4.2)
Adverse Events	0	1 (0.6)	1 (0.3)
-Ocular	0	0	0
-Non-ocular	0	1 (0.6)	1 (0.3)
Lack of efficacy	0	0	0
Pregnancy	0	0	0
Lost to follow-up	4 (2.4)	7 (4.2)	11 (3.3)
Personal reasons	0	0	0
Protocol violation	0	0	0
Other	0	2 (1.2)	2 (0.6)

a Includes all randomized subjects who are culture positive at baseline.

Reviewer's Comment:
Significant data integrity issues were found at Site 13020 which enrolled 72 patients of whom 31 were included in the mITT population.

The Subject Disposition data are presented without Site 13020 above and including Site 13020 below. There were no significant treatment group differences in Subject Disposition in either the ITT or mITT populations whether Site 13020 is included or excluded.

Table 6.2.3-4 Subjects Discontinued from Treatment or Study ITT Population

Reason for Discontinuation	Treatment	Center Number	Patient Number
Adverse event – Otitis media	Gatifloxacin 0.5%	10002	1769
Adverse event – Iritis	Gatifloxacin 0.5%	10007	1418
Adverse event – Worsening of anxiety and depression	Gatifloxacin 0.5%	10007	1727
Adverse event – Corneal epithelium defect	Gatifloxacin 0.5%	13010	1095
Adverse event – Viral keratitis	Gatifloxacin 0.5%	13010	1504
Adverse event – Superficial punctate keratitis	Gatifloxacin 0.5%	13030	1471
Adverse event – Otitis media	Vehicle	10001	1677
Adverse event – Adenovirus infection	Vehicle	10007	1854
Adverse event – Corneal epithelial erosion	Vehicle	13010	1068
Adverse event – Hordeolum	Vehicle	13010	1605
Lack of Efficacy [a]	Vehicle	13029	1010
Lost to Follow-up	Gatifloxacin 0.5%	13006	1061
Lost to Follow-up	Gatifloxacin 0.5%	13006	1080
Lost to Follow-up	Gatifloxacin 0.5%	13010	1107
Lost to Follow-up	Gatifloxacin 0.5%	13013	1468
Lost to Follow-up	Gatifloxacin 0.5%	13017	1182
Lost to Follow-up	Gatifloxacin 0.5%	13017	1564
Lost to Follow-up	Gatifloxacin 0.5%	13019	1352
Lost to Follow-up	Gatifloxacin 0.5%	13019	1380
Lost to Follow-up	Gatifloxacin 0.5%	13019	1730
Lost to Follow-up	Gatifloxacin 0.5%	13019	1737
Lost to Follow-up	Gatifloxacin 0.5%	13021	1110
Lost to Follow-up	Gatifloxacin 0.5%	13021	1118
Lost to Follow-up	Gatifloxacin 0.5%	13023	1238
Lost to Follow-up	Gatifloxacin 0.5%	13023	1484
Lost to Follow-up	Gatifloxacin 0.5%	13028	1534
Lost to Follow-up	Gatifloxacin 0.5%	13029	1831
Lost to Follow-up	Gatifloxacin 0.5%	13030	1609
Lost to Follow-up	Gatifloxacin 0.5%	13031	1051
Lost to Follow-up	Vehicle	10002	1851
Lost to Follow-up	Vehicle	13001	1085
Lost to Follow-up	Vehicle	13001	1479

Reason for Discontinuation	Treatment	Center Number	Patient Number
Lost to Follow-up	Vehicle	13006	1555
Lost to Follow-up	Vehicle	13010	1096
Lost to Follow-up	Vehicle	13010	1149
Lost to Follow-up	Vehicle	13010	1152
Lost to Follow-up	Vehicle	13013	1477
Lost to Follow-up	Vehicle	13017	1357
Lost to Follow-up	Vehicle	13019	1121
Lost to Follow-up	Vehicle	13019	1643
Lost to Follow-up	Vehicle	13019	1763
Lost to Follow-up	Vehicle	13021	1645
Lost to Follow-up	Vehicle	13023	1279
Lost to Follow-up	Vehicle	13023	1419
Lost to Follow-up	Vehicle	13026	1448
Lost to Follow-up	Vehicle	13027	1452
Lost to Follow-up	Vehicle	13028	1729
Lost to Follow-up	Vehicle	13029	1008
Lost to Follow-up	Vehicle	13030	1470
Other – Lost test drug bottle. Not willing to complete study	Vehicle	13010	1187
Other – Waiver not received for new kit. Patient did not receive treatment.	Vehicle	13021	1284
Personal reasons	Gatifloxacin 0.5%	10003	1184
Personal reasons	Gatifloxacin 0.5%	13010	1213
Personal reasons	Vehicle	13016	1473
Personal reasons	Vehicle	13029	1715
Protocol violation – Erroneous randomization; Positive adenovirus test	Gatifloxacin 0.5%	13023	1243
Protocol violation – Erroneous randomization; Positive adenovirus test	Vehicle	13020	1072
Withdrew consent [b]	Gatifloxacin 0.5%	10013	1893
Withdrew consent	Vehicle	13029	1015

a As determined by the subject
b Consent withdrawn by parent for child.

Reviewer's Comment:

There was no treatment group difference in study discontinuations due to adverse events. The majority of study discontinuations in both treatment groups were due to patients lost to follow-up.

Table 6.2.3-5 Randomized Subjects with Major Protocol Deviations Excluded from the Per Protocol Population

Protocol violation	Treatment Group	Center Number	Patient Number
Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10002	1823
Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10002	1894
Dosed beyond Day 5	Gatifloxacin 0.5%	10007	1514
Dosed beyond Day 5	Gatifloxacin 0.5%	10007	1633
Dosed beyond Day 5	Gatifloxacin 0.5%	10007	1776
Dosed beyond Day 5	Gatifloxacin 0.5%	10013	1665
Did not meet Inclusion Criterion 3	Gatifloxacin 0.5%	10016	1787
Day 6 visit > 48 hrs after last dose	Gatifloxacin 0.5%	10017	1765
Dosed for 4 days	Gatifloxacin 0.5%	13007	1494
Dosed for 4 days	Gatifloxacin 0.5%	13007	1495
Dosed beyond Day 5 Day 6 visit on same day as last dose	Gatifloxacin 0.5%	13010	1060
Dosed beyond Day 5	Gatifloxacin 0.5%	13011	1123
Dosed beyond Day 5	Gatifloxacin 0.5%	13013	1368
Dosed beyond Day 5	Gatifloxacin 0.5%	13015	1067
Randomization without IVRS – Dosed with two study kits: 60210 and 60229	Gatifloxacin 0.5%	13016	1019
Day 6 visit occurred 4 days after last dose	Gatifloxacin 0.5%	13016	1053
Dosed beyond Day 5	Gatifloxacin 0.5%	13017	1083
Dosed beyond Day 5	Gatifloxacin 0.5%	10032	1156
Screening failure randomized to kit 61395 which was not dispensed.	Gatifloxacin 0.5%	13023	1243
Use of preserved tears during study	Gatifloxacin 0.5%	13026	1354
Day 6 visit occurred 3 days after last dose	Gatifloxacin 0.5%	13027	1442
Dosed beyond Day 5	Gatifloxacin 0.5%	13028	1533
Dosed beyond Day 5	Vehicle	10001	1830
Day 6 visit occurred 8 days after last dose	Vehicle	10002	1848
Day 6 visit occurred 5 days after last dose	Vehicle	10002	1882
Did not meet Inclusion Criterion 3	Vehicle	10007	1461
Dosed beyond Day 5 Day 6 visit was > 48 hrs after last dose	Vehicle	10007	1508

Protocol violation	Treatment Group	Center Number	Patient Number
Dosed with prohibited concomitant medication Had signs/symptoms > 96 hrs before baseline exam	Vehicle	10007	1804
Did not meet Inclusion Criterion 3	Vehicle	10016	1786
Day 6 visit occurred 3 days after last dose	Vehicle	10017	1766
Day 6 visit occurred 4 days after last dose	Vehicle	10017	1785
Dosed beyond Day 5	Vehicle	13004	1023
Dosed beyond Day 5 Day 6 visit on same day as last dose	Vehicle	13010	1055
Dosed beyond Day 5 Day 6 visit on same day as last dose	Vehicle	13011	1103
Randomization without IVRS – Dosed with two study kits: 60169 and 60167. Dosed through Day 6	Vehicle	13012	1136
Day 6 visit occurred 3 days after last dose	Vehicle	13013	1453
Dosed beyond Day 5	Vehicle	13014	1230
Dosed through Day 4 only	Vehicle	13014	1840
Prohibited medication - Alphagan P throughout study	Vehicle	13014	1856
Day 6 visit occurred 3 days after last dose	Vehicle	13017	1608
Day 6 visit occurred 4 days after last dose	Vehicle	13019	1399
Dosed through Day 4	Vehicle	13019	1742
Screening failure randomized to kit 60463 which was not dispensed.	Vehicle	13020	1072
Randomization error – Kit 61427 incorrectly randomized. Subject did not receive kit and was discontinued.	Vehicle	13021	1284
Day 6 visit occurred 3 days after last dose	Vehicle	13023	1584
Dosed beyond Day 5	Vehicle	13025	1141
Dosed through Day 4	Vehicle	13025	1201
Prohibited medication – Pred Forte throughout study	Vehicle	13032	1747

Reviewer's Comment:

Twenty two patients in the gatifloxacin treatment group and twenty six patients in the vehicle treatment group had major protocol deviations which caused them to be excluded from the Per Protocol population. The majority of the protocol violations were related to incorrect dosing and follow-up visits outside the visit window.

6.2.4 Analysis of Primary Endpoint(s)

The primary efficacy variable was clinical success, defined as achievement of a score of zero for both conjunctival hyperemia and conjunctival discharge in the study eye. The primary efficacy assessment was based on the clinical success rate, defined as the proportion of patients who had achieved clinical success up to the day 6 time point.

The primary analysis for efficacy was revised prior to unblinding the study to the Up to Day 6 visit analysis in the mITT population, which included 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. This analysis method was defined by the visit window in the statistical analysis plan. The Day 6 visit analysis is considered secondary. The clinical success rate was compared between the gatifloxacin 0.5% and vehicle treatment groups using the Pearson's chi-square test.

Reviewer's Comment:
All efficacy results are those for the populations excluding Site 13020 due to the data integrity issues identified by the Applicant.

Table 6.2.4-1 Primary Efficacy Analysis Clinical Success in the Study Eye mITT Population

	Up to Day 6 Analysis (Primary Analysis Method)		
Population (Analysis) Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
mITT (LOCF)			
Day 4 n/N (%)	23/166 (13.9%)	17/167 (10.2%)	0.302
Day 6 n/N (%)	**86/166 (51.8%)**	**69/167 (41.3%)**	**0.055**

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, the Fisher's exact test was used.

Reviewer's Comment:
The proportion of patients who achieved clinical success in the modified Intent-to-Treat population was numerically greater in the gatifloxacin group compared to the vehicle group; it reaches marginal statistical significance in the Up-to-Day 6 analysis at p = 0.055.

See Section 6.2.10 (Additional Efficacy Issues/Analyses) for the supportive Day 6 analysis.

6.2.5 Analysis of Secondary Endpoints(s)

Microbiological Cure
The planned secondary efficacy endpoints were microbiological cure and clinical improvement. A conjunctival sample for bacterial culture and sensitivity was obtained from the qualified eye(s) at each visit, and was used to determine microbiological cure and microbiological response. A

patient was considered to have microbiological cure if all bacterial species present at Day 1 (baseline) were eradicated.

Table 6.2.5-1 Microbiological Cure in the Study Eye
mITT Population

	Up to Day 6 Visit Analysis (Primary Analysis Method)		
Visit / Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
Day 4 n/N (%)	144/166 (88.0%)	123/167 (73.3%)	< 0.001
Day 6 n/N (%)	153/166 (92.2%)	134/167 (80.2%)	0.002

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, the Fisher's exact test was used.

Reviewer's Comment:
The treatment group difference in microbiological cure in the study eye was statistically significant at the Day 6 time point.

Table 6.2.5-2
Microbiological Eradication in the Study Eye by Most Frequent Organisms
mITT Population

	Up to Day 6 Visit Analysis (Primary Analysis Method)			
Organism	**Gatifloxacin (N=166)**		**Vehicle (N=167)**	
	No. of infections	**No. of eradications (%)**	**# of infections**	**# of eradications**
Staphylococcus aureus	32	30 (93.8%)	20	15 (75.0%)
Staphylococcus epidermidis	26	24 (92.3%)	23	21 (91.3%)
Gram positive cocci, in clusters, isolated	7	4 (57.1%)	15	10 (66.7%)
Pseudomonas aeruginosa	6	6 (100.0%)	14	14 (100.0%)
Staphylococcus hominis	7	6 (85.7%)	14	14 (100.0%)

(b) (4)

Reviewer's Comment:
There was a higher percentage of microbiological eradications in the gatifloxacin group for each of the listed organisms except for Gram Positive cocci, in clusters, isolated and Staphylococcus hominis. *There were less than 10 infections for each of these organisms in the gatifloxacin group.*

6.2.6 Other Endpoints

No additional endpoints were required to establish the efficacy of the drug product.

6.2.7 Subpopulations

Subgroup analyses of the clinical success rate, the primary efficacy variable, were performed by age group in the mITT population, excluding site 13020, using Pearson's chi-square test or Fisher's exact test.

Table 6.2.7 Clinical Success in the Study Eye – Up to Day 6 Analysis [c]
mITT population (LOCF)

	Up to Day 6 Visit Analysis		
Age Group Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
1 – 5 years			
Day 4 n/N (%)	5/6 (83.3)	5/12 (41.7)	
Day 6 n/N (%)	6/6 (100.0)	7/12 (58.3)	0.515 [b]
6 – 10 years			
Day 4 n/N (%)	3/7 (42.9)	0/3 (00.0)	
Day 6 n/N (%)	6/7 (85.7)	1/3 (33.3)	0.183 [b]
11 – 15 years			
Day 4 n/N (%)	0/3 (00.0)	0/3 (00.0)	
Day 6 n/N (%)	2/3 (66.7)	0/3 (00.0)	0.400 [b]
16 – 17 years			
Day 4 n/N (%)	0/2 (00.0)	0/2 (00.0)	
Day 6 n/N (%)	1/2 (50.0)	1/2 (50.0)	> 0.999 [b]
1 – 17 years			
Day 4 n/N (%)	8/18 (44.4)	5/20 (25.0)	
Day 6 n/N (%)	15/18 (83.31)	11/20 (55.0)	0.061

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, then Fisher's exact test was used.
b Fisher's exact is used.
c Day 6 is the primary time point for the assessment of clinical success. Up to Day 6 analysis excludes data collected after day 6.

Reviewer's Comment:
For the overall pediatric population, patients age 1 – 17 years, the treatment group difference in the proportion of patients who achieved clinical success in the mITT population did not reach statistical significance at Day 4 or Day 6 (Day 6 visit analysis).

The treatment group differences did not reach statistical significance for any of described age groups (i.e., 1-5 years, 6 -10 years, 11-15 years or 16-17 years). These age groups were significantly underpowered.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The concentration of 0.5% gatifloxacin was chosen for Zymaxid based on the efficacy and safety of Zymar. The formulation was modified by an increase in the drug substance concentration, decreases in pH to ensure drug solubility and in the sodium chloride concentration for tonicity.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In both phase 3 trials, patients were evaluated at a test-of-cure visit approximately 60-90 hours following the last dose. No evidence of tolerance or withdrawal effects was detected.

6.2.10 Additional Efficacy Issues/Analyses

The results of an alternative analysis, the Day 6 visit analysis, which included all data collected for the Day 6 visit even if it was collected after Day 6 are presented below.

Table 6.2.10-1 Clinical Success in the Study Eye
Day 6 Visit Analysis

	Day 6 Visit Analysis		
Population (Analysis) Time point	**Gatifloxacin**	**Vehicle**	**p value [a]**
mITT (LOCF)			
Day 4 n/N (%)	23/166 (13.9%)	17/167 (10.2%)	0.302
Day 6 n/N (%)	99/166 (59.6%)	78/167 (46.7%)	0.018
PP			
Day 4 n/N (%)	23/155 (14.8%)	16/148 (10.8%)	0.295
Day 6 n/N (%)	93/156 (59.6%)	72/146 (49.3%)	0.072
ITT (LOCF)			
Day 4 n/N (%)	65/394 (16.5%)	58/393 (14.8%)	0.502
Day 6 n/N (%)	226/394 (57.4%)	199/393 (50.6%)	0.058

a P value is from Pearson's chi-square test, unless ≥ 25% of the cells had expected counts < 5, the Fisher's exact test was used.

Reviewer's Comment:
In the Day 6 Visit analysis, the proportion of patients who achieved clinical success in the modified Intent-to-Treat population (LOCF) at Day 6 was greater in the gatifloxacin group compared to the vehicle group. The treatment group difference in proportions reached statistical significance in these populations with p=0.018.

Table 6.2.10-2 Clinical Success and Microbiological Cure by Organism in the Study Eye at the Day 6 Time Point (mITT Population without Site 13020)

Organism	Up to Day 6 Visit Analysis			
	Gatifloxacin n/N (%)		Vehicle n/N (%)	
	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure
Staphylococcus aureus	16/32 (50.0)	30/32 (93.8)	8/24 (33.3)	16/24 (66.7)
Staphylococcus epidermidis	15/28 (53.6)	26/28 (92.9)	8/18 (44.4)	17/18 (94.4)
(b) (4)				
Gram positive cocci in clusters [a]	6/12 (50.0)	7/12 (58.3)	10/22 (45.5)	12/22 (54.5)
(b) (4)				
Staphylococcus hominis	3/7 (42.9)	7/7 (100)	7/15 (46.7)	15/15 (100)
Pseudomonas aeruginosa	2/6 (33.3)	5/6 (83.3)	3/9 (33.3)	9/9 (100)
Mixed infection total [b]	6/14 (42.9)	12/14 (85.7)	11/25 (44.0)	18/25 (72.0)

N= number of patients with that organism present above threshold in the study eye at baseline
a These organisms were not identified to the genus species level, therefore it was not possible to determine whether or not mixed infection was present in an individual patient.
b Patients with mixed infection are not included in rows for individual organisms.

Reviewer's Comment:
There were ≥ 10 isolates with at least a 50% clinical success rate of Staphylococcus aureus, Staphylococcus epidermidis, and (b) (4)*. There were no organisms with between 5 and 9 isolates with at least an 80% clinical success rate.*

Table 6.2.10-3
Clinical Success and Microbiological Cure [a] in the Study Eye
by Organism at the Day 6 Time Point
(Pooled mITT Population, LOCF)

Organism	Up to Day 6 Visit Analysis			
	Gatifloxacin n/N (%)		Vehicle n/N (%)	
	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure
Gram Positive bacilli isolated [b]	2/5 (40.0)	5/5 (100)	0/0 (0.0)	0/0 (0.0)
Gram positive cocci in clusters [b]	6/12 (50.0)	7/12 (58.3)	10/22 (45.5)	12/22 (54.5)
Haemophilus influenzae	38/43 (88.4)	42/43 (97.7)	19/45 (42.2)	26/45 (57.8)
(b) (4)				
Pseudomonas aeruginosa	2/7 (28.6)	6/7 (85.7)	4/10 (40.0)	9/10 (90.0)
Staphylococcus aureus	26/52 (50.0)	45/52 (86.5)	13/37 (35.1)	22/37 (59.5)
Staphylococcus epidermidis	21/35 (60.0)	31/35 (88.6)	14/27 (51.9)	22/27 (81.5)
(b) (4)				
Staphylococcus hominis	3/7 (42.9)	7/7 (100)	7/15 (46.7)	15/15 (100)
Staphylococcus warneri	5/11 (45.5)	10/11 (90.9)	1/2 (50.0)	2/2 (100)
(b) (4)				
Streptococcus oralis	2/5 (40.0)	4/5 (80.0)	1/4 (25.0)	4/4 (100)
Streptococcus pneumoniae	21/34 (61.8)	30/34 (88.2)	22/38 (57.9)	24/38 (63.2)

Organisms were included if there were ≥ 5 patients in the gatifloxacin group with only that organism present above threshold at baseline and an evaluable result at the day 6 time point.
N= number of patients with that organism present above threshold in the study eye at baseline and an evaluable response at the day 6 time point
Patients with mixed infection are not included.
a Microbiological cure = all bacterial species present above threshold in the study eye at baseline were eradicated.
b These organisms were not identified to the genus and species level.

Reviewer's Comments:

Efficacy defined as clinical success based on the number of isolates seen, e.g. 5-9 isolates with ≥ 80% clinical success or ≥10 isolates with ≥ 50% clinical success, was demonstrated in patients with cultures positive for these known ophthalmic pathogens: Staphylococcus aureus,

Staphylococcus epidermidis, [redacted](b) (4), *Streptococcus pneumoniae, and Haemophilus influenzae.*

The applicant proposed inclusion of [redacted](b) (4) *in the product label. However, since no isolates of these ocular pathogens were cultured from the gatifloxacin-treated patients in the U.S. study, they should not be included in the product label.*

Table 6.2.10-4
Clinical Success and Microbiological Cure [a] in the Study Eye at the Day 6 Time Point by Organism in Selected Mixed Infections (Pooled mITT Population, LOCF)

Organism	Up to Day 6 Visit Analysis			
	Gatifloxacin n/N (%)		Vehicle n/N (%)	
	Clinical Success	Microbiological Cure	Clinical Success	Microbiological Cure
Streptococcus mitis group	8/9 (88.9)	9/9 (100)	3/4 (75.0)	3/4 (75.0)
Streptococcus oralis	5/7 (71.4)	6/7 (85.7)	1/2 (50.0)	1/2 (50.0)

Includes organisms that were identified in ≤ 5 single organism infections in the gatifloxacin group and ≥ 5 mixed infections in the gatifloxacin group.
N= number of patients with that organism present above threshold in the study eye at baseline and an evaluable response at the day 6 time point
Microbiological cure = all bacterial species present above threshold in the study eye at baseline were eradicated.

Reviewer's Comments:

When organisms that were identified in ≤ 5 single organism infections in the gatifloxacin group and ≥ 5 mixed infections in the gatifloxacin group are combined, Streptococcus mitis group and Streptococcus oralis meet the efficacy requirement defined as clinical success based on the number of isolates seen, e.g. 5-9 isolates with ≥ 80% clinical success or ≥10 isolates with ≥ 50% clinical success.

Thus, efficacy was demonstrated in patients with cultures positive for:

Gram-positive microorganisms: Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis group, Streptococcus oralis*, and Streptococcus pneumoniae.*

Aerobic and facultative Gram-negative microorganisms: Haemophilus influenzae.

**Efficacy of this organism was studied in fewer than 10 infections.*

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
198782-004 Safety and Efficacy Study	Randomized, double-masked, vehicle-controlled, parallel group, 2-arm, multicenter	Patients at least 1 year of age with acute bacterial conjunctivitis	Gatifloxacin 0.5% ophthalmic solution Vehicle	Day 1: 1 drop 8 up to 8 times Days 2 – 5: 1 drop BID	5 days with evaluation on following day	578
198782-005 Safety and Efficacy Study						859

7.1.2 Categorization of Adverse Events

The routine clinical testing required to establish the safety of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse events were evaluated individually for each study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety database includes all randomized and treated patients, 717 patients treated with gatifloxacin 0.5% and 716 patients treated with vehicle.

Table 7.2.1-1 Overview of Exposure to Study Drug by Protocol

Study Number	Safety N	Gatifloxacin 0.5%	Vehicle
198782-004	577	288	289
198782-005	856	429	427

Table 7.2.1-2 Summary of Exposure of Qualified and Unqualified Eyes by Patient Safety Population

	Study 198782-004 N=577		Study 198782-005 N=856	
	Gatifloxacin 0.5%	Vehicle	Gatifloxacin 0.5%	Vehicle
Number of Patients	288	289	429	427
2 Eyes Qualified	140 (48.6%)	123 (42.6%)	116 (27.0%)	101 (23.7%)
1 Eye Qualified	148 (51.4%)	166 (57.4%)	313 (73.0%)	326 (76.3%)
1 Eye Unqualified	148 (51.4%)	166 (57.4%)	313 (73.0%)	326 (76.3%)
Eye treated starting at baseline	0	1 (0.3%)	0	0
Eye treated at follow-up visit [a]	13 (4.5%)	11 (3.8%)	5 (1.2%)	22 (5.2%)
Eye Untreated	135 (46.9%)	154 (53.3%)	308 (71.8%)	304 (71.2%)

a Patients with an unqualified eye at baseline who were later diagnosed with bacterial conjunctivitis prior to day 6 were eligible for study medication treatment during the course of the study.

Reviewer Comment:
All adverse event analyses were based on the number of patients in the safety population and not on the number of eyes. Therefore, a patient may have been included in both the analysis of treated and untreated eyes.

7.2.2 Explorations for Dose Response

Gatifloxacin 0.5% was administered in one dosage regimen. One drop was instilled up to 8 times per day on Day 1 and twice daily on Days 2 through 5 in each of the phase 3 studies. No dose response information was obtained.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with gatifloxacin 0.5% ophthalmic solution. Adequate nonclinical investigations of gatifloxacin ophthalmic solution were performed for and submitted in the original NDA 21-493 for Zymar (gatifloxacin ophthalmic solution) 0.3%.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Adequate nonclinical investigations of gatifloxacin ophthalmic solution were performed for and submitted in the original NDA 21-493 for Zymar (gatifloxacin ophthalmic solution) 0.3%.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported during the development of gatifloxacin ophthalmic solution 0.5% are consistent with other topical quinolones. The assessment of these adverse events within the clinical trials was adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in either Study 198782-004 or Study 198782-005.

7.3.2 Nonfatal Serious Adverse Events

Two patients experienced serious adverse events (1 in the gatifloxacin group and 1 in the vehicle group).

> In the vehicle group in Study 198782-004, patient 10006-1357 experienced congestive heart failure.
>
> In the gatifloxacin group in Study 198782-005, patient 10007-1727 was hospitalized for worsening depression and anxiety one day after beginning study medication. This patient had a history of depression and anxiety. Study medication was stopped and the patient was discontinued from the study.

7.3.3 Dropouts and/or Discontinuations

Table 7.3.3-1 Patient Discontinuations (Safety Population)

	Study 198782-004 N=577		Study 198782-005 N=856	
	Gatifloxacin 0.5%	Vehicle	Gatifloxacin 0.5%	Vehicle
Safety Population [a]	288	289	429	427
Completed, N (%)	277 (96.2%)	275 (95.2%)	402 (93.7%)	398 (93.2%)
Discontinued, N (%)	11 (3.8%)	14 (4.8%)	27 (6.3%)	39 (6.8%)
Adverse Events	2 (0.7%)	5 (1.7%)	6 (1.4%)	4 (0.9%)
-Ocular	2 (0.7%)	5 (1.7%)	4 (0.9%)	3 (0.7%)
-Non-ocular	0	0	2 (0.5%)	1 (0.2%)
Lack of efficacy	2 (0.7%)	2 (0.7%)	0	0
Pregnancy	0	0	0	0
Lost to follow-up	3 (1.0%)	0	18 (4.2%)	20 (4.7%)
Personal reasons	0	3 (1.0%)	2 (0.5%)	2 (0.5%)
Protocol violation	1 (0.3%)	0	0	0
Other [b, c]	3 (1.0%)	4 (1.4%)	1 (0.2%)	3 (0.7%)

a Safety population includes all randomized patients who received at least one dose of study medication. Patients are analyzed according to the medication actually received.
b Study 198782-004 - Other reasons were withdrawn consent (n=2) and visit schedule conflict (n=1) for the gatifloxacin group and patient withdrew consent (n=3) and non-compliance (n=1) for the vehicle group.
b Study 198782-005 - Other reasons were withdrawn consent (n=1) for the gatifloxacin group and withdrawn consent / lack of efficacy (n=2) and patient lost study medication (n=1) for the vehicle group.

A table of the adverse events associated with the discontinuations is presented Sections 6.1.3 and 6.2.3. Based on a review of the Case Report Forms, it does not appear that the other discontinuations were due to adverse events. The "lost to follow-up" is unusually high for a one week study.

There were no significant treatment group differences in study discontinuations due to adverse events.

Refer to Table 6.1.3-4 and Table 6.2.3-6 for listings of patients discontinued from the study for all reasons. The majority of study discontinuations in both treatment groups were due to patients lost to follow-up.

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns

No specific primary safety concerns were identified for the submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 7.4.1-1 Adverse Events Occurring in ≥ 1% of Patients in Any Treatment Group Study 198782-004 – Safety Population

Preferred Term [a]	Gatifloxacin (N=288)	Vehicle (N=289)	p value [b]
Conjunctivitis bacterial	14 (4.9%)	13 (4.5%)	0.837
Pyrexia	4 (1.4%)	1 (0.3%)	0.216 [c]
Pharyngolaryngeal pain	3 (1.0%)	1 (0.3%)	0.373 [c]
Conjunctivitis	2 (0.7%)	4 (1.4%)	0.686 [c]
Headache	2 (0.7%)	4 (1.4%)	0.686 [c]
Eyelid edema	2 (0.7%)	3 (1.0%)	>0.999 [c]
Eye pruritus	1 (0.3%)	4 (1.4%)	0.373 [c]
Lacrimation increased	1 (0.3%)	4 (1.4%)	0.373 [c]
Otitis media	0	3 (1.0%)	0.249 [c]

a MedDRA version 10.0
b Pearson's chi square unless otherwise specified
c Fisher's exact test

Table 7.4.1-2 Adverse Events Occurring in ≥ 1% of Patients in Any Treatment Group Study 198782-005 – Safety Population

Preferred Term [a]	Gatifloxacin (N=429)	Vehicle (N=427)	p value [b]
Eye irritation	14 (3.3%)	7 (1.6%)	0.125
Dysgeusia	8 (1.9%)	1 (0.2%)	0.038 [c]
Eye pain	6 (1.4%)	8 (1.9%)	0.584
Conjunctivitis bacterial	5 (1.2%)	19 (4.4%)	0.004
Instillation site irritation	5 (1.2%)	0 (0.0%)	0.062 [c]
Conjunctivitis	0 (0.0%)	5 (1.2%)	0.031 [c]

a MedDRA version 10.0
b Pearson's chi square unless otherwise specified
c Fisher's exact test

Reviewer's Comment:
There were no significant treatment group differences in adverse events in Study 198782-004.

The occurrence of 'bacterial conjunctivitis' and 'conjunctivitis' was more frequent and statistically significant in the vehicle group compared to the gatifloxacin group. These events likely reflect the decreased efficacy of the vehicle compared to gatifloxacin.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were not performed in either Study 198782-004 or Study 198782-005.

7.4.3 Vital Signs

Vital signs were not evaluated in either Study 198782-004 or Study 198782-005.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in either Study 198782-004 or Study 198782-005.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies conducted for this product in either Study 198782-004 or Study 198782-005.

7.4.6 Immunogenicity

Immunogenicity testing was not conducted in either Study 198782-004 or Study 198782-005.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Gatifloxacin ophthalmic solution 0.5% was administered in one dose level (One drop every 2 hours up to 8 times on Day 1 and 1 drop twice a day on Days 2 through 5) for each of the phase 3 studies. No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

Gatifloxacin does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

Demographic subgroups with and without adverse events were sorted by age, gender, race, ethnicity. Based on a review of adverse events by these subgroups, the events are consistent with the overall safety population.

7.5.4 Drug-Disease Interactions

A review of adverse events revel no untoward safety issues in each of the subpopulations categorized by concomitant diseases.

7.5.5 Drug-Drug Interactions

Systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly.

Systemic exposure with gatifloxacin ophthalmic solution is minimal. In an 11-day phase 1 study in healthy adults there were no detectable ($\geq$ 5 ng/mL) serum levels of gatifloxacin following ophthalmic administration with concentrations as high as 0.5% and administration as frequent as 2 drops given 8 times daily. This Study Report (Study Report SJC-7001/1-01-PC) was submitted in NDA 21-493 Zymar (gatifloxacin ophthalmic solution, 0.3%) on May 29, 2002.

No pharmacokinetic data were collected in the phase 3 Studies 198782-004 and 198782-005.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were conducted and submitted in the original NDA 21-493 for Zymar (gatifloxacin ophthalmic solution) 0.5%.

7.6.2 Human Reproduction and Pregnancy Data

The clinical development program for gatifloxacin excluded the participation of pregnant or breast-feeding females. There have been no clinical studies in human reproduction or pregnancy performed. No clinical study or post-marketing data suggest an effect on human reproduction or pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Based on the review of the original NDA for Zymar (gatifloxacin ophthalmic solution, 0.3%), there is no evidence that the ophthalmic administration of gatifloxacin has any effect on weight

bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential for abuse with gatifloxacin.

7.7 Additional Submissions

The 120 day safety update was submitted on November 20, 2009. No additional safety data from studies 198782-004 or 198782-005 were submitted. Allergan is not conducting any other clinical studies at this time related to the proposed indication for this NDA. Allergan has submitted updated post-marketing data for Zymar (gatifloxacin ophthalmic solution) 0.3%.

8 Postmarket Experience

Gatifloxacin ophthalmic solution 0.5% is not marketed in any country. Zymar (gatifloxacin ophthalmic solution, 0.3% was approved in the U.S. in 2003.

In the most recent annual Periodic Safety Update Report for Zymar (gatifloxacin ophthalmic solution) 0.3%, fifty-eight case reports involving 111 adverse event terms were reported worldwide associated with gatifloxacin. Thirty-five (35) were confirmed by healthcare professionals including 17 which were considered serious and 18 non-serious. The spontaneous postmarketing reports for gatifloxacin are consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with gatifloxacin.

9 Appendices

9.1 Literature Review/References

An independent literature review did not produce any additional significant information regarding gatifloxacin.

9.2 Advisory Committee Meeting

An advisory committee meeting is not required for this application.

9 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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05/14/2010

WILLIAM M BOYD
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carton