CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-493

MICROBIOLOGY REVIEW

Product Quality Microbiology Review
Review for HFD-550

16 July 2002

NDA: 21-493

Drug Product Name
Proprietary: —— Ophthalmic Solution
Non-proprietary: Gatifloxacin Ophthalmic Solution
Drug Product Classification: Ophthalmic Antibiotic

Review Number: 1

Subject of this Review
Submission Date: 29 May 2002
Receipt Date: 30 May 2002
Consult Date: 06 June 2002
Date Assigned for Review: 25 June 2002

Applicant/Sponsor
Name: Allergan
Address: 2525 DuPont Drive, P.O. Box 19534, Irvine, CA 92623
Representative: Elizabeth Bancroft
Telephone: (714)246-4391

Name of Reviewer: Paul Stinavage

Conclusion: The application is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Waco, TX and Westport, County Mayo, Ireland

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 0.3%

5. **METHOD(S) OF STERILIZATION:** Aseptic fill

6. **PHARMACOLOGICAL CATEGORY:** Ophthalmic antibiotic

B. **SUPPORTING/RELATED DOCUMENTS:** NDA 21-061, NDA 21-062, IND [redacted]

C. **REMARKS:** All product configurations ([redacted] 2.5 mL, and 5 mL) will be manufactured at both facilities.

filename: n21493.doc

APPEARS THIS WAY
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Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

II. Summary of Microbiology Assesments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Container\closure components are sterilized using [redacted] The product is aseptically filled into sterilized containers.

B. Brief Description of Microbiology Deficiencies -

C. Assessment of Risk Due to Microbiology Deficiencies -

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
P. Stinavage
P.H. Cooney

C. CC Block
cc:
Original NDA 21-493
HFD-550/Division File/NDA 21-493/L. Gorski

8 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Wiley Chambers
2/8/02 11:47:06 AM

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ON ORIGINAL

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

Consultative Review for HFD-550
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products

Requestor: Lori Gorski, PM, CSO HFD-550

Date of Request: June 14, 2002

Reason for Request: Original NDA—request comments on clinical microbiology issues

NDA #: 21-493

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	29-MAY-02
CDER DATE:	30-MAY-02
REVIEW ASSIGN DATE:	18-JUN-02
REVIEW COMPLETE DATE:	23-AUG-02

SPONSOR:
Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

CONTACT PERSON:
Elizabeth Bancroft
Sr. Director, Regulatory Affairs
Phone Number: (714) 246-4391

SUBMISSION REVIEWED: Original NDA

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Bacterial Conjunctivitis

DOSAGE FORM: Sterile ophthalmic solution

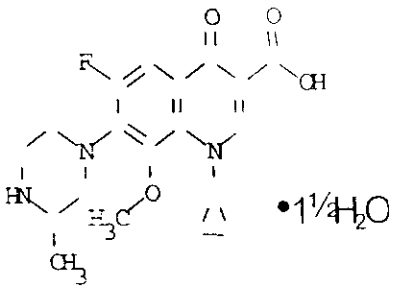
DRUG PRODUCT NAME

PROPRIETARY: —

NONPROPRIETARY/USAN: Gatifloxacin ophthalmic solution

CHEMICAL NAME: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate

STRUCTURAL FORMULA:



Molecular Formula: $C_{19}H_{22}FN_3O_4 \bullet 1\frac{1}{2}\ H_2O$
Molecular Weight: 402.42

SUPPORTING DOCUMENTS: [redacted]

NDA 21-061—Gatifloxacin Tablets
NDA 21-062—Gatifloxacin IV

REMARKS/COMMENTS:

This application is for a 0.3% gatifloxacin ophthalmic solution. The proposed indication for the product is the treatment of bacterial conjunctivitis, in both adults and children 1 year of age or older. The proposed dosing regimen is one drop every 2 hours up to 8 times a day on days 1 and 2, and one drop every 4 hours up to 4 times a day on days 3 through 5.

Two pivotal studies have been performed to support this indication. Study SPCL-GFLX 3/01 evaluated the safety and efficacy of 0.3% gatifloxacin ophthalmic solution used for 5 days versus placebo in 265 patients. Study SPCL-GFLX 3/02 evaluated a 5 day regimen of gatifloxacin compared to ofloxacin 0.3% ophthalmic solution in 459 patients.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when the recommended changes are made to the MICROBIOLOGY subsection of the package insert. The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 49-53.

Microbiological Review

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Bacterial conjunctivitis is a common eye disease encountered by the ophthalmologist. The treatment regimen usually involves the use of an antimicrobial agent to control or manage the disease. Antimicrobial therapy usually proves beneficial by removing the etiological agents and reducing the ocular signs of the disease. The most frequent bacterial causes include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

Data from the original gatifloxacin NDAs that were collected in the late 1990's produced the MICs summarized in TABLE A. The susceptible breakpoint for most pathogens in systemic infections is ≤2.0 µg/mL.

TABLE A
In vitro Activity of Gatifloxacin in Original NDAs 21-061 and 21-062

Pathogen	United States No. Isolates Tested	United States MEAN MIC_{90} (µg/mL)	Foreign No. Isolates Tested	Foreign MEAN MIC_{90} (µg/mL)
Bacillus species	10	0.12	0	
Enterococcus faecalis	781	>4	589	6.8
Staphylococcus aureus MS	368	0.11	1389	0.25
Staphylococcus aureus MR	2744	>4	1642	6.2
Staphylococcus epidermidis MS	32	0.12	101	1.6
Staphylococcus epidermidis MR	307	1.9	198	5.9
Staphylococcus haemolyticus MS	11	0.12	34	0.5
Staphylococcus haemolyticus MR	36	6.9	45	2
Streptococcus agalactiae	169	0.5	85	0.5
Streptococcus mitis	48	0.5	0	
Streptococcus pneumoniae	2356	0.5	643	0.5
Streptococcus pyogenes	141	0.5	202	0.6
Viridans streptococci	655	0.5	92	0.25
Streptococcus groups C,G,F	82	0.5	82	0.5
Acinetobacter baumannii	126	>4	277	3.9
Acinetobacter lwoffii	53	0.8	83	0.05
Enterobacter cloacae	472	1.4	340	>4
Escherichia coli	2553	0.06	1801	6.6
Haemophilus influenzae	1422	≤0.03	410	0.01
Klebsiella pneumoniae	923	0.02	731	3.3
Morganella morganii	63	2.1	188	0.3
Neisseria gonorrhoeae	166	0.06	238	0.05
Proteus mirabilis	245	1.9	285	1.1
Proteus vulgaris	18	1	201	0.4
Providencia rettgeri	17	1	119	13
Pseudomonas aeruginosa	1257	>4	1103	>4
Serratia marcescens	227	3.0	291	10
Bacteroides fragilis	177	3.5	249	4.8

MS = methicillin-susceptible; MR = methicillin-resistant

Gatifloxacin has good activity against methicillin-susceptible staphylococci. It has poor activity against methicillin-resistant staphylococci. It has good activity against most streptococci. Gatifloxacin has varied activity against *Acinetobacter* species. It has excellent activity against *Haemophilus influenzae* and *Neisseria gonorrhoeae*. It has variable activity against most Gram-negative bacteria.

In the Phase III clinical studies conjunctiva swab specimens from patients were done and pathogens were identified. Due to the self-limiting nature of bacterial conjunctivitis an endpoint evaluation at the end of therapy may not be optimal for comparative evaluation of efficacy. An evaluation following 3 days of therapy was done to allow some treatment differences to be distinguished. A final evaluation (test-of-cure) was also performed on day 6. A microbiological cure was achieved when all pathogens above threshold count values in the conjunctival swab sample at baseline were eradicated. Microbiological cure rates are summarized in TABLE B.

TABLE B
Summary of Microbiological Cure
(Phase III, Per Protocol Population)

	SPCL-GFLX 3/01		SPCL-GFLX 3/02	
	Gatifloxacin N=52	Placebo N = 48	Gatifloxacin N = 78	Ofloxacin N= 69
DAY 3				
success	39 (88.6%)	20 (48.8%)	60 (82.2%)	53 (80.3%)
failure	5 (11.4%)	21 (51.2%)	13 (17.8%)	13 (19.7%)
DAY 6				
success	48 (92.3%)	34 (72.3%)	65 (83.3%)	58 (85.3%)
failure	4 (7.7%)	13 (27.7%)	13 (16.7%)	10 (14.7%

TABLE C shows the same information for the modified intent-to-treat (mITT) population.

TABLE C
Summary of Microbiological Cure
(Phase III, mITT Population)

	SPCL-GFLX 3/01		SPCL-GFLX 3/02	
	Gatifloxacin N=69	Placebo N = 58	Gatifloxacin N = 103	Ofloxacin N= 100
DAY 3				
success	51 (85.0%)	25 (50.0%)	81 (82.7%)	79 (79.8%)
failure	9 (15.0%)	25 (50.0%)	17 (17.3%)	20 (20.2%)
DAY 6				
success	62 (89.9%)	40 (69.0%)	86 (83.5%)	81 (81.0%)
failure	7 (10.1%)	18 (31.0%)	17 (16.5%)	19 (19.0%)

Gatifloxacin was better than placebo at both days 3 and 6 and equivalent to ofloxacin.

TABLE D shows the eradication rate by organism (for the most common species) in the Phase III trials.

TABLE D
Eradication Rates at Day 6
(Phase III Studies, per Protocol Population)

	SPCL-GFLX 3/01		SPCL-GFLX 3/02	
	Gatifloxacin	**Placebo**	**Gatifloxacin**	**Ofloxacin**
Bacterial Classification				
All organisms	92.9% (65/70)	79.1% (53/67)	86.7% (85/98)	88.6% (78/88)
Gram positive bacteria	92.7% (51/55)	72.0% (36/50)	81.8% (54/66)	86.6% (58/67)
Gram negative bacteria	93.3% (14/15)	100% (17/17)	96.9% (31/32)	95.2% (20/21)
Species				
Haemophilus influenzae	100% (10/10)	100% (13/13)	96.2% (25/26)	100% (14/14)
Staphylococcus aureus	100% (13/13)	62.5% (5/8)	100% (9/9)	78.6% (11/14)
Staphylococcus epidermidis	88.9% (8/9)	53.3% (8/15)	70.6% (12/17)	84.2% (16/19)
Streptococcus pneumoniae	90.0% (9/10)	50.0% (4/8)	70.0% (14/20)	84.2% (16/19)

Gatifloxacin was better than placebo. This difference is due to better eradication of Gram positive bacteria. It appears that most Gram negative bacterial infections were resolved without antibiotic treatment. Gatifloxacin and ofloxacin appear to be equivalent.

Three animal model studies of ocular diseases were performed to evaluate the efficacy of gatifloxacin. Two of the studies showed efficacy against ocular infections in rabbits caused by methicillin-resistant *Staphylococcus aureus*. The other study showed efficacy against *Pseudomonas* keratitis in rabbits.

After ocular administration gatifloxacin blood levels were below the limit of detection ———. Following ocular administration to rabbits, gatifloxacin distributed to all parts of the eye with the highest concentrations in the cornea and conjunctiva.

PRECLINICAL EFFICACY

MODE OF ACTION

The sponsor has provided several literature sources on the mechanism of action of gatifloxacin and quinolones in general. These reference do not provide any new information. The information in the proposed labeling is identical to that in the tablet and intravenous label which is approved.

Gatifloxacin is an 8-methoxyfluoroquinolone. It appears that the C-8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram positive bacteria compared to the non-methoxy C-8 moiety. The antibacterial action of gatifloxacin and the other quinolones results from inhibition of DNA gyrase and topoisomerase IV, both type II topoisomerases. DNA gyrase is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV plays a role in partitioning of the chromosomal DNA during bacterial cell division.

Gyrase consists of two subunits, GyrA and GyrB, encoded by the *gryA* and *gyrB* genes, respectively. The active enzyme is an A_2B_2 complex. The GyrA subunit is responsible for breakage and reunion of DNA and is the target of quinolones. The GyrB subunit is involved in the ATP activated passage of one DNA segment through the double-stranded break. Gyrase binds to DNA and a segment of approximately 130 base pairs (130 bp) is wrapped around the protein. This wrapped DNA is cleaved in both strands, with a 4-base stagger between break sites, which results in the formation of DNA-protein covalent bonds between the GyrA subunits and the 5'-phosphates on the DNA molecule. Another segment of DNA is passed through the double-stranded break which may then be resealed. The quinolone drugs interrupt this process at the DNA breakage-reunion step.

In the beginning it was shown that nalidixic acid was an inhibitor of bacterial DNA replication. Prior to the discovery of DNA gyrase, a number of possible targets were found not to be inhibited by nalidixic acid. Following the isolation of gyrase from *Escherichia coli* by Gellert (1) it was shown that its supercoiling activity could be inhibited by oxolinic acid (2,3). Moreover, gyrase extracted from a nalidixic acid-resistant mutant was found to be resistant to oxolinic acid. Since then a large number of quinolone-resistance mutations have been mapped to the gyrase genes, principally to *gyrA* (4,5,6). This lead to the belief that gyrase was the principle target of quinolones.

In recent years the existence of a second target, DNA topoisomerase IV, has been established. Like gyrase, topoisomerase IV is a bacterial type II DNA topoisomerase. It cannot supercoil DNA, however. Topoisomerase IV carries out the ATP-dependent relaxation of DNA and has been found to be a more potent decatenase than DNA gyrase (7,8). This enzyme is composed of two subunits, which in *E. coli* are encoded by the *parC* and *parE* genes. The *parC* gene encodes the ParC subunit and the *parE* gene encodes the ParE subunit. Originally it was thought that *E. coli* DNA topoisomerase IV was not readily inhibited by the fluoroquinolones since 30 times more drug was required to inhibit topoisomerase IV mediated relaxation than to inhibit relaxation by DNA gyrase (9). It has now been shown (8) that fluoroquinolones may have significant activity against topoisomerase IV mediated decatenation of DNA.

Ferrero (10) demonstrated using resistant isolates that topoisomerase IV is a primary target of fluoroquinolones in *Staphylococcus aureus*. Isolates with high levels of resistance were found to have mutations in both *gryA* and *grlA* (equivalent to *parC* in *E. coli*). Clinical isolates with low level resistance were found to have mutations in only *grlA* (11). Analysis of quinolone resistance in *E. coli* (12,13) revealed that topoisomerase IV is likely a secondary target. These studies were unable to detect resistance associated with ParC alone. These data lead to the conclusion that the quinolones primary target is gyrase in Gram negative bacteria and topoisomerase IV in Gram positive bacteria. In *Streptococcus pneumoniae*, gyrase has been shown to be the primary target of gatifloxacin, although gatifloxacin also had activity against topoisomerase IV equal to or greater than that of ciprofloxacin (14). This may indicate that the structure of the drug molecule and not the type of bacteria may determine the primary cellular target. Some of the newer fluoroquinolones, such as gatifloxacin, have less preference for one target over the other. This suggests that mutations in both gyrase and topoisomerase IV genes would be necessary for resistance. In *Staphylococcus aureus*, gatifloxacin had activity against DNA gyrase that was equal or nearly equal to its activity against topoisomerase IV (15,16,17).

EXECUTIVE SUMMARY

Background:

Gatifloxacin has been approved under NDA 21-061 and NDA 21-062 (Bristol-Myers Squibb) as Tequin® (gatifloxacin) 200 mg and 400 mg tablets and 100 mL (200 mg) and 200 mL (400 mg) injection. Indications approved are treatment of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute sinusitis, uncomplicated urinary tract infections (cystitis), complicated urinary tract infections, acute pyelonephritis, uncomplicated urethral gonorrhea in men, and endocervical or rectal gonorrhea in women.

This application NDA 21-493 is for Gatifloxacin 0.3% ophthalmic solution for the treatment of bacterial conjunctivitis.

Dosing and Administration:

Oral or IV doses of gatifloxacin that can be used for various indications vary from 200-400 mg daily for 1-14 days. For most indication the dose is 400 mg for 7-10 days.

The ophthalmic dose for the treatment of bacterial conjunctivitis is:
Days 1 and 2: 1 drop every two hours in the affected eye(s), up to 8 times daily
Days 3-5: 1 drop up to 4 times daily.

Considering a drop size of 35µL, a total of 0.84 mg of gatifloxacin will be administered daily for the first two days of ocular dosing, subsequently up to 5 days 0.42 mg of gatifloxacin will be administered through the ocular route. These doses are much lower than the oral or IV doses.

Formulation:

Component	Concentration (% w/v)	Concentration (mg/mL)
Gatifloxacin (Anhydrous Basis)	0.3	3.0
Benzalkonium chloride	0.005	[redacted]
Edetate Disodium	[redacted]	[redacted]
Sodium Chloride	[redacted]	[redacted]
Hydrochloric Acid or Sodium Hydroxide	[redacted]	
Purified Water	q.s. ad to 100%	q.s. ad to 1 mL

Systemic Absorption of Gatifloxacin after Topical Ocular Dosing:

Systemic absorption of gatifloxacin 0.3% and 0.5% has been evaluated after single and repeat topical ocular dosing in six healthy adult male volunteers for each concentration (Study No. SJC7001/1-01-PC):

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The sponsor has provided some literature studies on the activity of gatifloxacin. These papers do not add any new information. TABLE 1 gives a summary of the *in vitro* data provided in the tablet and intravenous NDA submissions for gatifloxacin.

TABLE 1
In vitro Activity of Gatifloxacin in Original NDAs 21-061 and 21-062

Pathogen	United States No. Isolates Tested	United States MEAN MIC_{90} (µg/mL)	Foreign No. Isolates Tested	Foreign MEAN MIC_{90} (µg/mL)
Bacillus species	10	0.12	0	
Enterococcus faecalis	781	>4	589	6.8
Staphylococcus aureus MS	368	0.11	1389	0.25
Staphylococcus aureus MR	2744	>4	1642	6.2
Staphylococcus epidermidis MS	32	0.12	101	1.6
Staphylococcus epidermidis MR	307	1.9	198	5.9
Staphylococcus haemolyticus MS	11	0.12	34	0.5
Staphylococcus haemolyticus MR	36	6.9	45	2
Streptococcus agalactiae	169	0.5	85	0.5
Streptococcus mitis	48	0.5	0	
Streptococcus pneumoniae	2356	0.5	643	0.5
Streptococcus pyogenes	141	0.5	202	0.6
Viridans streptococci	655	0.5	92	0.25
Streptococcus groups C,G,F	82	0.5	82	0.5
Acinetobacter baumannii	126	>4	277	3.9
Acinetobacter lwoffii	53	0.8	83	0.05
Enterobacter cloacae	472	1.4	340	>4
Escherichia coli	2553	0.06	1801	6.6
Haemophilus influenzae	1422	≤0.03	410	0.01
Klebsiella pneumoniae	923	0.02	731	3.3
Morganella morganii	63	2.1	188	0.3
Neisseria gonorrhoeae	166	0.06	238	0.05
Proteus mirabilis	245	1.9	285	1.1
Proteus vulgaris	18	1	201	0.4
Providencia rettgeri	17	1	119	13
Pseudomonas aeruginosa	1257	>4	1103	>4
Serratia marcescens	227	3.0	291	10
Bacteroides fragilis	177	3.5	249	4.8

MS = methicillin-susceptible; MR = methicillin-resistant

The data in the above table demonstrate that gatifloxacin has good activity against methicillin-susceptible staphylococci. Its activity against methicillin-resistant staphylococci is not very good. It has poor activity against enterococci. It has good activity against most streptococci. It has varying activity against *Enterobacteriaceae*. It has excellent activity against *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Its activity against *Acinetobacter* varies by species. It has poor activity against *Pseudomonas aeruginosa* and *Bacteroides fragilis*.

TABLE 2 is a summary of data provided in this submission on the activity of gatifloxacin against *Staphylococcus* species. These data are comparable to those in the original NDAs, which showed good activity against methicillin-susceptible strains, but poor to like activity against methicillin-resistant strains. Gatifloxacin's activity appears to be slightly better (2-4 times) than that of ofloxacin and ciprofloxacin against these species.

TABLE 2
MIC_{90} Values against Staphylococci

Organism	No. of Isolates	Gatifloxacin	Ciprofloxacin	Ofloxacin
S. aureus MS	27	0.12	0.5	0.25
S. aureus MR	58	4	32	16
S. epidermidis MS	32	0.12	0.5	0.5
S. epidermidis MR	35	2	32	16
S. haemolyticus MS	11	0.12	0.25	0.5
S. haemolyticus MR	17	8	>32	>32
S. saprophyticus MS	26	0.25	1	1

MS = Methicillin Susceptible; MR = Methicillin Resistant

TABLE 3 gives a summary of the sponsor's data for other Gram positive organisms. These data demonstrate that gatifloxacin is generally 4- to 8-fold more active than ofloxacin and ciprofloxacin against streptococci, enterococci, *Listeria monocytogenes*, and other miscellaneous Gram positive bacteria. Gatifloxacin appears to have limited activity against *Enterococcus faecium*.

TABLE 3
MIC_{90} Values against Gram Positive Organisms other than Staphylococci

Organism	No. of Isolates	Gatifloxacin	Ciprofloxacin	Ofloxacin
S. pyogenes	10	0.5	1	2
S. agalactiae	10	0.5	2	4
S. mitis	17	0.5	4	4
S. sanguis	18	1	4	4
Streptococcus Groups C, F, G	16	0.5	2	2
S. pneumoniae Pen MIC <0.1µg/mL	10	0.5	2	4
S. pneumoniae Pen MIC 0.1 to 1 µg/mL	10	0.5	4	4
S. pneumoniae Pen MIC >1µg/mL	10	0.5	4	4
E. faecalis	18	1	2	8
E .faecium	14	4	8	16
L. monocytogenes	26	0.5	1	2
G. vaginalis	11	0.5	2	2

TABLE 4 gives a summary of the sponsor's data for *Enterobacteriaceae*. These data demonstrate that gatifloxacin has activity about equal to that of ofloxacin and about 2-fold less than that of ciprofloxacin for most of these organisms. Against *Providencia* species, gatifloxacin has better activity than the comparator drugs.

TABLE 4
MIC_{90} Values against *Enterobacteriaceae*

Organism	No. of Isolates	Gatifloxacin	Ciprofloxacin	Ofloxacin
E. coli	18	0.06	0.016	0.06
K. pneumoniae	18	0.25	0.25	0.5
K. oxytoca	18	0.06	0.03	0.12
E. cloacae	18	0.12	0.03	0.12
E. aerogenes	17	0.12	0.06	0.12
C. fruendii	18	0.5	0.25	1
C. diversus	18	0.12	0.06	0.25
S. marcescens	18	0.5	0.25	0.5
P. mirabilis	18	0.5	0.12	0.5
P. vulgaris	18	1	0.12	0.5
M. morganii	18	0.25	0.06	0.25
P. stuartii	18	4	16	>16
P. rettgeri	17	1	4	2
Salmonella spp.	18	0.06	0.03	0.12
Shigella spp.	18	0.03	0.03	0.06
V. cholerae	13	0.008	0.004	0.016
Y. enterocolitica	15	0.03	0.03	0.12
A. hydrophila	16	0.06	0.016	0.06

TABLE 5 gives a summary of the sponsors data for other Gram negative bacteria. Gatifloxacin is 2-fold less active than ciprofloxacin against *Pseudomonas aeruginosa*. Gatifloxacin appears to have limited activity against *Pseudomonas aeruginosa*. Activity against *Burkholderia cepacia* and *Stenotrophomonas maltophilia* is also limited at best, but is equal to that of the comparators. Against *Acinetobacter* species, gatifloxacin has slightly better activity than ciprofloxacin. Gatifloxacin's activity against *Haemophilus influenzae, Moraxella catarrhalis, Neisseria* species, *Bordetella* species, *Legionella* species, and *Helicobacter pylori* is excellent and equal to or better than that of ciprofloxacin and ofloxacin.

TABLE 5
MIC_{90} Values Against Gram Negative Bacteria (Other than *Enterobacteriaceae*

Organism	No. of Isolates	Gatifloxacin	Ciprofloxacin	Ofloxacin
C. jejuni	12	0.12	0.12	0.25
A. baumanii	18	1	2	2
A. lwoffi	18	0.5	1	1
P. aeruginosa	18	4	2	4
B. cepacia	18	8	8	8
S. maltophilia	18	4	8	8
Neisseria gonorrheae BLA-	17	0.016	0.03	0.03
Neisseria gonorrheae BLA+	18	0.03	0.016	0.12
N. meningitidis	35	0.008	008	0.016
H. influenzae BLA-,+	35	0.03	0.03	0.06
M. catarrhalis	35	0.12	0.12	0.12
Flavobacterium spp.	17	1	4	4
Bordetella spp.	14	0.03	0.12	0.12
Legionella spp.	25	0.03	0.12	0.12
Helicobacter pylori	10	0.06	0.06	0.12

TABLE 6 gives a summary of the sponsor's data on gatifloxacin's activity against anaerobic bacteria. In general gatifloxacin had better activity than ciprofloxacin or ofloxacin, especially against *Bacteroides* species.

TABLE 6
MIC_{90} Values against Anaerobic Bacteria

Organism	No. of Isolates	Gatifloxacin	Ciprofloxacin	Ofloxacin
B. fragilis	18	1	16	8
B. thetaiotaomicron	12	2	32	16
Fusobacterium spp.	13	4	4	8
Clostridium perfringens	18	0.5	1	1
Clostridium difficile	25	1	16	8
Peptostreptococcus spp.	17	1	4	8
Propionibacterium spp.	17	0.25	1	1

In the Phase III studies, MICs to gatifloxacin were determined for all pathological organisms. The sensitivity to gatifloxacin of the most common organisms (>5 isolates) at baseline is summarized for all treatment groups combined in TABLE 7. The values seen in the Phase III studies are in general comparable to those seen in *in vitro* studies.

TABLE 7
Minimum Inhibitory Concentration (µg/mL) to Gatifloxacin
At Baseline (Phase III Studies—All enrolled patients)

Organism	No. of Isolates	MIC (µg/mL) to Gatifloxacin		
		Minimum	Maximum	MIC_{90}
Corynebacterium propinquum	5			1.0
Haemophilus influenzae	93			0.03
Moraxella catarrhalis	5			0.06
Serratia marcescens	7			1.0
Staphylococcus aureus	71			0.25
Staphylococcus capitis	11			2.0
Staphylococcus epidermidis	94			2.0
Staphylococcus hominis	8			4.0
Staphylococcus warneri	5			2.0
Streptococcus mitis	20			0.5
Streptococcus oralis	14			1.0
Streptococcus pneumoniae	78			0.5
Streptococcus salivarius	7			0.5
Streptococcus sanguis	5			0.5

MECHANISMS OF RESISTANCE STUDIES

The primary mechanisms of bacterial resistance to fluoroquinolones can be attributed to mutations in the *gryA* and *parC/grlA* genes. Mutations in the *gyrB* gene also may confer resistance but to a lesser extent than mutations in the *gyrA* gene. Other factors such as diminished uptake due to: (a) multiantibiotic resistance (MAR locus), (b) porin-deficiency, (c) changes in lipopolysaccaride content, and (d) efflux mechanisms (such as *norA*) can also lead to resistance.

Overexpression of the staphylococcal NorA efflux pump resulted in gatifloxacin MIC increases of 2- to 8-fold. This increase is less than the 15- to 60-fold increase observed with ciprofloxacin, norfloxacin, or ofloxacin. Sparfloxacin only had a 3-fold increase.

In *Staphylococcus aureus,* high-level resistance to gatifloxacin requires mutations in both amino acids 80 and 84 of GrlA, as well as amino acid 84 of GyrA. A mutation in the quinolone resistance-determining region (QRDR) of each *gryA* and *grlA* suffice in producing a fairly high-level of resistance to gatifloxacin. Mutations in the *grlA* gene alone produce low-level gatifloxacin resistance. A mutation in the *gryA* gene alone usually does not produce a change in the MIC. It appears that gatifloxacin, like most other fluoroquinolones, has topoisomerase IV as its primary target in *S. aureus.*

The QRDR in the *gryA* gene in *Escherichia coli* encodes amino acids 67-106. The mutational "hot spots" for most quinolones are the *gyrA* codons 83 and 87. Double mutations result in high level resistance in quinolones. A single *gyrA* mutation can lead to significant increases in MIC. Changes in the *parC* gene alone usually do not lead to a significant change in gatifloxacin MIC. In Gram negative bacteria gatifloxacin and most other fluoroquinolones have DNA gyrase as their primary target.

Mutations in the target genes increase MICs for all quinolones. Mutants that have high nalidixic acid MICs also usually have increased gatifloxacin MICs, but these MICs may still be below the achievable levels of gatifloxacin in many fluids and tissue and, therefore, may still be susceptible to gatifloxacin. Resistance to one quinolone does not necessarily imply resistance to all quinolones.

The concept of dual targets and accumulation of resistance mutations in a stepwise manner has important implications for 8-methoxyfluoroquinolones such as gatifloxacin, because they have enhanced activity against first-step mutants, especially in Gram positive bacteria (18). 8-methoxyfluoroquinolones may restrict selection of resistant mutants in wild-type populations because these agents require simultaneous double mutations for resistance to occur. These double mutations occur at extremely low rates in wild-type strains previously unexposed to fluoroquinolones (18,19). Dual *gyrA* and *parC* mutations were described in clinical isolates of *S. pneumoniae*, but it is thought that these strains were selected by fluoroquinolones with less potent anti-pneumococcal activity (20).

Compared to ciprofloxacin and levofloxacin, gatifloxacin is less likely to allow resistant mutants to arise in Gram positive bacteria. Once resistant mutants do appear gatifloxacin has better activity than ciprofloxacin or levofloxacin against these strains (21).

The 8-methoxy group of gatifloxacin seems to confer a decreased frequency of mutation to resistance (22). To quantify this, the concept of the mutant prevention concentration (MPC) was devised. The MPC is the concentration of antibiotic at which no resistant mutants appear when a large number of bacterial cells are in the presence of the antibiotic (23). Measurements of MPC for gatifloxacin against *Mycobacterium tuberculosis* were 1.0 to 1.5 µg/mL, whereas the MPC for ciprofloxacin was 6.0 to 8.0 µg/mL. MPCs for non-fluoroquinolones such as rifampin, streptomycin, isoniazid, kanamycin, and cycloserine ranged from 20 to 400 µg/mL, reflecting the much higher frequency at which resistance to these drugs arises. For a collection of clinical isolates of *Streptococcus pneumoniae*, the MPC_{90} values (the antibiotic concentration at which 90% of the input strains cannot form resistant mutants) were 4 µg/mL for gatifloxacin and 8 µg/mL for levofloxacin (24). Ciprofloxacin has poor activity against *S. pneumoniae* and was not tested. The low MPC values for gatifloxacin are thought to reflect the fact that gatifloxacin targets both gyrase and topoisomerase IV almost equally in *Staphylococcus* and *Streptococcus* species. In contrast, ciprofloxacin and levofloxacin target mostly topoisomerase IV in these Gram positive bacteria.

Reports of plasmid-mediated quinolone resistance are rare (25,26). In the first published study (25) on this phenomenon (1987), it was reported that a plasmid found in *Shigella dysenteriae* from an outbreak in Bangladesh was able to transfer nalidixic acid resistance to *E. coli*. In retrospect, the presumed transconjugants were probably resistant mutants, because they were selected with nalidixic acid and had no other

plasmid-mediated resistances. In the second more recent paper (26) a plasmid from *Klebsiella pneumoniae* was described that carries resistance to a number of antibiotics. In this study quinolones were not used to obtain transconjugants, so there was no risk of selection of quinolone-resistant host mutants. In wild-type strains, resistance was low, but in certain clinical isolates deficient in outer-membrane porins the plasmid raised quinolone resistance to more than 256 µg/mL. Generally this plasmid facilitated selection of higher quinolone resistance but did not enhance mutations. Attempts to show decreased quinolone accumulation or drug inactivation by this plasmid have been uninformative. It probably does not provide a quinolone-resistant DNA gyrase or DNA topoisomerase IV, since the chromosomal allele would be dominant and result in quinolone susceptibility. The mechanism of action of this plasmid is, therefore, a mystery at the present time.

Enzymatic inactivation of quinolones by bacteria has never been reported.

It is possible to select resistant mutants with gatifloxacin by multiple passages through subinhibitory concentrations. This is true with most antibacterial agents. This multi-step resistance is not as significant as high-level resistance from single-step mutation, but it may be predictive of the consequences of long-term therapy with subtherapuetic doses or at sites where the drug does not penetrate well. This should not be a major problem with this ophthalmic dosage since the level of drug in tear fluid is usually high with ophthalmic solutions. A study performed by Schmitz (27) showed that the rate of increase in MIC per day for *Streptococcus pneumoniae* exposed to subinhibitory concentrations of gatifloxacin was about twice as slow as the increase when this species was exposed to ciprofloxacin.

PRECLINICAL EFFICACY (*IN VIVO*)

PHARMACOKINETICS/BIOAVAILABILITY

Gatifloxacin ophthalmic solution (0.3%) is to be dosed as one drop in the affected eye(s) every 2 hours while awake up to 8 times per day on days 1 and 2 and then one drop up to four times daily while awake on days 3 through 5.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

In an attempt to characterize the clinical pharmacokinetics of gatifloxacin following ocular dosing, 0.3% and 0.5% ophthalmic solutions were administered to healthy subjects. Following a maximum of eight times daily dosing, serum gatifloxacin levels were below the assay lower limit of detection ——— in all subjects, indicating that gatifloxacin serum concentrations were uniformly low following ocular dosing.

No information seems to have been submitted on the concentration of gatifloxacin in ocular tissue after administration in humans. Following ocular administration to rabbits, gatifloxacin distributed to all parts of the eye and achieved relatively high concentrations in the cornea and conjunctiva of rabbits. In both Dutch and Japanese White rabbits, higher concentrations were observed in the conjunctiva, cornea, and aqueous humor (ranging from) than in the lens, vitreous humor, and retina (ranging from) following a single ocular dose.

ANIMAL PROPHYLACTIC AND THERAPEUTIC STUDIES

Three studies were performed in ocular disease models to evaluate the efficacy of gatifloxacin ophthalmic solution against two of the most common organisms causing ocular infections, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

In the first study (28) the efficacy of gatifloxacin was compared with that of ofloxacin in rabbit corneas injected with methicillin-resistant *Staphylococcus aureus* (MRSA). Gatifloxacin 0.5%, ofloxacin 0.3% or saline was administered topically at 5, 12, 20 and 28 hours after the bacterial inoculation, and the infection was monitored macroscopically at 8, 16, 24, 32, 48, and 72 hours post-inoculation. Both gatifloxacin and ofloxacin were effective in reducing the signs of the infection beginning at hour 16 and continuing through the duration (72 hours) of the study.

The second study (29) was a dose ranging evaluation of gatifloxacin conducted in the MRSA model described in the above study. In this study gatifloxacin at 0.02%, 0.1%, 0.3%, and 0.5% were compared to ofloxacin at 0.3%. The antibacterial formulations were dosed ocularly at 5 and 24 hours post-inoculation. Gatifloxacin, in a dose-dependent fashion, decreased signs of corneal infection, with no difference in efficacy between 0.3% and 0.5%. The antibacterial effect of ofloxacin was approximately equal to 0.1% gatifloxacin and inferior to 0.3% and 0.5% gatifloxacin. A reduction in viable bacteria as a result of gatifloxacin treatment was dose dependent and all concentrations, except the 0.02% gatifloxacin concentration) were more effective than ofloxacin. Histopathological abnormalities were observed in the saline-treated group but not in the 0.3% and 0.5% gatifloxacin groups and in the ofloxacin group. Gatifloxacin was effective in this model at concentrations $\geq$0.3%.

In the third report (30), the efficacy of 0.3% gatifloxacin was evaluated in a *Pseudomonas aeruginosa* corneal ulcer model in rabbits. Four treatment regimens using gatifloxacin 0.3% were compared to ciprofloxacin 0.3%. The first instillation of drug was 24 hours post-inoculation and the study was 23 days long. All conjunctival cultures were negative for *Pseudomonas aeruginosa* when tested on day 22 post-inoculation. Administration of gatifloxacin 0.3%, at any of the given dosing regimes was as effective as ciprofloxacin 0.3% in this study.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

Two Phase III clinical trials are presented in this NDA.

Study SPCL-GFLX 3/01—Phase III clinical and microbiological evaluation of 0.3% gatifloxacin ophthalmic solution versus placebo for the treatment of bacterial conjunctivitis.

Study SPCL-GLX 3/02—Phase III clinical and microbiological evaluation of 0.3% gatifloxacin ophthalmic solution versus 0.3% ofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis.

The dosing regimen used in the Phase III studies was 1 to 2 drops administered every 2 hours while awake for the first 2 days (maximum of 8 applications per day), followed by administration 4 times daily (every 4 hours while awake) for 3 additional days. This regimen is what is common for marketed fluoroquinolone ophthalmic solutions. The frequent instillation is trying to get early eradication of the bacterial pathogen. The clinical trails used a 5 day regimen (±1 day) instead of the usual 7 days. It was expected that the 5 days would be enough to treat the conjunctivitis and also shorten the course of antimicrobial treatment, which might prevent the emergence of resistant strains and avoid some adverse events.

Due to the self-limiting nature of bacterial conjunctivitis, endpoint evaluations after 7 days of therapy may not be optimal for the comparison of efficacy. The studies, therefore, included an early evaluation at day 3 as well as a final evaluation on day 6. Efficacy measures were based on microbiological cultures and the clinical assessment of four ophthalmic signs and symptoms. The primary efficacy endpoint was clinical cure on day 6. Secondary efficacy endpoints were clinical cure on day 3, clinical improvement on days 3 and 6, change from baseline for each sign and symptom on days 3 and 6, and microbiological cure on days 3 and 6. Microbiological cure was defined as the eradication of all pathogens that were present above threshold count values at baseline. Efficacy analyses were performed for both the per protocol and modified intent-to-treat populations. The per protocol (PP) population consisted of all enrolled patients who had a positive bacteriological culture at baseline and who did not have a protocol deviation. The modified intent-to-treat (mITT) population consisted of all enrolled patients who received study drug and had at least one post-baseline efficacy measure.

STUDY SPCL-GFLX 3/01

A total of 265 patients were enrolled in study 3/01: 134 patients in the gatifloxacin group and 131 in the placebo group. TABLE 8 shows the patient disposition for this study.

TABLE 8
Patient Disposition (study 3/01)

Analysis Population Disposition	Gatifloxacin	Placebo
Safety Population	134	131
Completed	123 (91.8%)	124 (94.7%)
Discontinued	11 (8.2%)	7 (5.3%)
Adverse event	3 (2.2%)	1 (0.8%)
Treatment failure	2 (1.5%)	3 (2.3%)
Other	6 (4.5%)	3 (2.3%)
Per Protocol Population	52	48
Modified ITT Population	133	128

The primary reasons for patient discontinuation in the safety population were as follows: treatment failure—1.5% (2/134) of gatifloxacin and 2.3% (3/131) of placebo patients; adverse events—2.2% (3/134) of gatifloxacin and 0.8% (1/131) of placebo patients; consent withdrawn—2.2% (3/134) of gatifloxacin and 0.8% (1/131) of placebo patients.

There were 165 patients excluded from the per protocol (PP) population for one or more of the following reasons:

- 46.3% (62/134) of gatifloxacin patients and 52.7% (69/131) of placebo patients were not culture positive at baseline
- 19.4% (26/134) of gatifloxacin patients and 19.8% (26/131) of placebo patients did not have a day 6 visit with a culture sample that was 12 to 24 hours after their last dose of study medication
- 6.7% (9/134) of gatifloxacin patients and 3.1% (4/131) of placebo patients did not receive the full course of therapy
- 3.0% (4/134) of gatifloxacin patients and 3.8% (5/131) of placebo patients received prohibited concomitant medications during the study
- 1.5% (2/134) of gatifloxacin patients and 1.5% (2/131) of placebo patients had their current episode of conjunctivitis >4 days duration
- 0.7% (1/134) of gatifloxacin patients and 2.3% (3/131) of placebo patients had an average ophthalmic sign score <2 at baseline
- 1.5% (2/134) of gatifloxacin patients and 1.5% (2/131) of placebo patients had no source documentation
- 0 gatifloxacin patients and 0.8% (1/131) of placebo patients sensitivity to test drugs was not recorded at baseline
- 4 patients were misrandomized: 3 patients were assigned gatifloxacin and received placebo; 1 patient was assigned placebo and received gatifloxacin

There were four patients who were excluded from the mITT population: 2.2% (3/134) of gatifloxacin patients and 0.8% (1/131) of placebo patients had no postbaseline efficacy assessments. The four patients who were misrandomized were included in the mITT population and analyzed according to their intended randomized treatment.

TABLE 9 gives a summary of the microbiological results in the per protocol (PP) population.

TABLE 9
Summary of Microbiological Cure
(Per Protocol Population)

Microbiological Cure[a]	Gatifloxacin N = 52	Placebo N = 48
Day 3	N = 44	N = 41
Success	39 (88.6%)	20 (48.8%)
Failure	5 (11.4%)	21 (51.2%)
Day 6	N = 52	N = 47
Success	48 (92.3%)	34 (72.3%)
Failure	4 (7.7%)	13 (27.7%)

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

At day 3, of the five gatifloxacin patients who failed, 3 patients showed reduction, 1 persistence, and 1 proliferation. Of the 21 placebo patients who failed, 1 showed reduction, 15 persistence, and 5 proliferation.

At day 6, of the four gatifloxacin patients who failed, 1 showed reduction, and 3 persistence; no gatifloxacin patient had proliferation at day 6. Of the 13 placebo patients who failed, 5 patients showed reduction, 6 persistence, and 2 proliferation.

Microbiological cure with gatifloxacin was evident by day 3 when the success rate was 39.9% higher with gatifloxacin than with placebo. At day 6, the eradication rate was 20.0% higher with gatifloxacin than with placebo.

TABLE 10 shows the eradication rates by organism in the per protocol population.

TABLE 10
Microbiological Response by Bacterial Classification
(Per Protocol Population)

Organism	Day	Gatifloxacin		Placebo	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
All Organisms	3	61	56 (91.8%)	56	33 (58.9%)
	6	70	65 (92.9%)	67	53 (79.1%)
Gram Positive Bacteria	3	50	45 (90.0%)	43	24 (55.8%)
	6	55	51 (92.7%)	50	36 (72.0%)
Gram Negative Bacteria	3	11	11 (100.0%)	13	9 (69.3%)
	6	15	14 (93.3%)	17	17 (100.0%)
A. calcoaceticus-	3	0		0	
A. baumannii	6	1	1 (100.0%)	0	
Corynebacterium	3	1	1 (100.0%)	1	1 (100.0%)
group G	6	1	1 (100.0%)	1	1 (100.0%)
Corynebacterium	3	1	1 (100.0%)	0	
macginleyi	6	1	1 (100.0%)	0	
Corynebacterium	3	1	1 (100.0%)	1	1(100.0%)
propinquum	6	1	1 (100.0%)	1	1 (100.0J%)
Corynebacterium	3	1	1 (100.0%)	0	
species	6	1	1 (100.0%)	0	
Enterobacter	3	0		1	1 (100.0%)
agglomerans	6	0		1	1 (100.0%)
Enterobacter sakazakii	3	0		0	
	6	1	1 (100.0%)	0	
Enterobacter durans	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Enterococcus faecalis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Haemophilus influenzae	3	9	9 (100.0%)	11	7 (63.6%)
	6	10	10 (100.0%)	13	13 (100.0%)
Haemophilus	3	1	1 (100.0%)	0	
parainfluenzae	6	1	1 (100.0%)	0	
Klebsiella pneumoniae	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Moraxella catarrhalis	3	0		0	
	6	0		2	2 (100.0%)
Pseudomonas	3	1	1 (100.0%)	0	
aeruginosa	6	1	1 (100.0%)	0	
Pseudomonas putida	3	0		0	
	6	1	0 (0.0%)	0	
Rothia dentocariosa	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Rothia species	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)

TABLE 10 (continued)
Microbiological Response by Bacterial Classification
(Per Protocol Population)

Organism	Day	Gatifloxacin		Placebo	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
Staphylococcus aureus	3	12	11 (91.7%)	6	5 (83.3%)
	6	13	13 (100.0%)	8	5 (62.5%)
Staphylococcus capitis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Staphylococcus epidermidis	3	8	5 (62.5%)	13	4 (30.8%)
	6	9	8 (88.9%)	15	8 (53.3%)
Staphylococcus haemolyticus	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Staphylococcus hominis	3	1	1 (100.0%)	2	1 (50.0%)
	6	1	1 (100.0%)	2	2 (100.0%)
Staphylococcus simulans	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Staphylococcus warneri	3	3	3 (100.0%)	0	
	6	3	2 (66.7%)	0	
Stomatococcus mucilaginosus	3	2	2 (100.0%)	0	
	6	2	1 (50.0%)	0	
Streptococcus acidominimus	3	0		0	
	6	0		1	1 (100.0%)
Streptococcus anginosus	3	0		0	
	6	1	1 (100.0%)	0	
Streptococcus gordonii	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus mitis	3	5	5 (100.0%)	1	1 (100.0%)
	6	5	5 (100.0%)	1	1 (100.0%)
Streptococcus oralis	3	1	1 (100.0%)	3	3 (100.0%)
	6	1	1 (100.0%)	4	4 (100.0%)
Streptococcus parasanguis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus pneumoniae	3	8	7 (87.5%)	8	0 (0.0%)
	6	10	9 (90.0%)	8	4 (50.0%)
Streptococcus salivarius	3	0		1	1 (100.0%)
	6	0		2	2 (100.0%)
Streptococcus sanguis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Streptococcus species	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus vestibularis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus nutrition variable	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	

The data in the above table demonstrate that most of the difference in eradication rates between gatifloxacin and placebo is due to differences in efficacy in the Gram positive population. This is especially noticeable against *Streptococcus pneumoniae*. There were no pathogens at baseline that were resistant to gatifloxacin.

In the per protocol (PP) population the organisms that occurred greater than five times and were treated with gatifloxacin were *Haemophilus influenzae* (10/10 eradicated), *Staphylococcus aureus* (13/13 eradicated), *Staphylococcus epidermidis* (8/9 eradicated), *Streptococcus mitis* (5/5 eradicated), and *Streptococcus pneumoniae* (9/10 eradicated).

TABLE 11 gives a summary of the microbiological results in the modified intent-to-treat (mITT) population.

TABLE 11
Summary of Microbiological Cure
(mITT Population)

Microbiological Cure[a]	Gatifloxacin N = 133	Placebo N = 128
Day 3	N = 60	N = 50
Success	51 (85.0%)	25 (50.0%)
Failure	9 (15.0%)	25 (50.0%)
Day 6	N = 69	N = 58
Success	62 (89.9%)	40 (69.0%)
Failure	7 (10.1%)	18 (31.0%)

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

Microbiological cure with gatifloxacin was evident by day 3 when the success rate was 35.0% higher with gatifloxacin than with placebo. At day 6, the eradication rate was 20.9% higher with gatifloxacin than with placebo.

TABLE 12 shows the eradication rates by organism in the mITT population.

TABLE 12
Microbiological Response by Bacterial Classification
(mITT Population)

Organism	Day	Gatifloxacin		Placebo	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
All Organisms	3	85	76 (89.4%)	71	41 (57.7%)
	6	95	87 (91.6%)	88	67 (76.1%)
Gram Positive Bacteria	3	65	56 (86.2%)	53	30 (56.6%)
	6	70	63 (90.0%)	66	48 (72.7%)
Gram Negative Bacteria	3	20	20 (100.0%)	18	11 (61.1%)
	6	25	24 (96.0%)	22	19 (86.4%)
A. calcoaceticus-	3	0		1	0 (0.0%)
A. baumannii	6	1	1 (100.0%)	1	0 (0.0%)
Actinomyces odontolyticus	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Bacillus species	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Corynebacterium group G	3	1	1 (100.0%)	1	1 (100.0%)
	6	1	1 (100.0%)	1	1 (100.0%)
Corynebacterium macginleyi	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Corynebacterium propinquum	3	1	1 (100.0%)	1	1 (100.0%)
	6	1	1 (100.0%)	1	1 (100.0%)
Corynebacterium species	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Enterobacter agglomerans	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Enterobacter cloacae	3	0		0	
	6	1	1 (100.0%)	0	
Enterobacter sakazakii	3	0		0	
	6	1	1 (100.0%)	0	
Enterobacter durans	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Enterococcus faecalis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Haemophilus influenzae	3	15	15 (100.0%)	14	8 (57.1%)
	6	16	16 (100.0%)	16	13 (81.3%)
Haemophilus parahaemolyticus	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Haemophilus parainfluenzae	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Klebsiella pneumoniae	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Moraxella catarrhalis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	2	2 (100.0%)
Moraxella species	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Pseudomonas aeruginosa	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Pseudomonas putida	3	0		0	
	6	1	0 (0.0%)	0	
Rosemonas species	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Rothia dentocariosa	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Rothia species	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)

TABLE 12 (continued)
Microbiological Response by Bacterial Classification
(mITT Population)

Organism	Day	Gatifloxacin		Placebo	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
Serratia liquefaciens	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Serratia marcescens	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Staphylococcus aureus	3	16	14 (87.5%)	7	6 (85.7%)
	6	17	16 (94.1%)	9	6 (66.7%)
Staphylococcus capitis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Staphylococcus epidermidis	3	10	6 (60.0%)	17	5 (29.4%)
	6	11	8 (72.7%)	22	12 (54.5%)
Staphylococcus haemolyticus	3	0		3	3 (100.0%)
	6	0		3	3 (100.0%)
Staphylococcus hominis	3	1	1 (100.0%)	2	1 (50.0%)
	6	1	1 (100.0%)	2	2 (100.0%)
Staphylococcus lugdunensis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Staphylococcus simulans	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Staphylococcus warneri	3	3	3 (100.0%)	0	
	6	3	2 (66.7%)	0	
Stomatococcus mucilaginosus	3	4	4 (100.0%)	1	1 (100.0%)
	6	4	3 (75.0%)	1	1 (100.0%)
Streptococcus acidominimus	3	0		0	
	6	0		2	2 (100.0%)
Streptococcus anginosus	3	0		0	
	6	1	1 (100.0%)	0	
Streptococcus gordonii	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus intermedius	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus mitis	3	9	9 (100.0%)	2	1 (50.0%)
	6	9	9 (100.0%)	2	1 (50.0%)
Streptococcus oralis	3	3	2 (66.7%)	5	5 (100.0%)
	6	3	2 (66.7%)	6	6 (100.0%)
Streptococcus parasanguis	3	3	3 (100.0%)	0	
	6	3	3 (100.0%)	0	
Streptococcus pneumoniae	3	9	7 (77.8%)	9	1 (11.1%)
	6	11	10 (90.9%)	10	5 (50.0%)
Streptococcus salivarius	3	0		2	1 (50.0%)
	6	0		4	3 (75.0%)
Streptococcus sanguis	3	1	1 (100.0%)	2	1 (50.0%)
	6	1	1 (100.0%)	2	1 (50.0%)
Streptococcus species	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	1	1 (100.0%)
Streptococcus uberis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus vestibularis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus nutrition variable	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	

Once again it can be seen that most of the difference in eradication rates between gatifloxacin and placebo (especially at day 6) is due to the difference seen when Gram positive bacteria are the pathogen. This is especially true with *Streptococcus pneumoniae*. This indicates that many of the other pathogens that cause conjunctivitis will be eliminated by the body's defense mechanisms and no antibiotics are needed.

In the intent-to-treat (mITT) population the organisms that occurred greater than five times and were treated with gatifloxacin were *Haemophilus influenzae* (16/16 eradicated), *Staphylococcus aureus* (16/17 eradicated), *Staphylococcus epidermidis* (8/11 eradicated), *Streptococcus mitis* (9/9 eradicated), and *Streptococcus pneumoniae* (10/11 eradicated).

For all organisms isolated from gatifloxacin patients in the mITT population at baseline which had MICs determined and for which interpretive criteria have been established, 100% (69/69) were susceptible to gatifloxacin. However 1.6% (1/64), 2.1% (2/97), and 1.4% (1/74) of these organisms were not susceptible to ciprofloxacin, levofloxacin, and ofloxacin, respectively. Almost all of these pathogens were, therefore, susceptible to all fluoroquinolones. At the end of treatment (Day 6 visit) organisms that were not eradicated were all susceptible to gatifloxacin (17/17), but 22.7% (5/22), 14.3% (4/28), and 22.7% (5/22) were not susceptible to ciprofloxacin, levofloxacin, and ofloxacin, respectively.

For all organisms isolated from the placebo patients in the mITT population at baseline which had MICs determined and for which interpretive criteria have been established, 98.6% (71/72) were susceptible to gatifloxacin. However 10.4% (7/67), 6.3% (6/96), and 11.8% (9/76) of these organisms were not susceptible to ciprofloxacin, levofloxacin, and ofloxacin, respectively. At the end of treatment 97.4% (38/39) of the organisms that were not eradicated were susceptible to gatifloxacin, but 11.8% (4/34), 8.5% (4/47), and 14.6% (6/41) were not susceptible to ciprofloxacin, levofloxacin, and ofloxacin, respectively. TABLE 13 summarizes the MIC data for the six isolates in the mITT population that were not susceptible to gatifloxacin.

TABLE 13
Organisms with Intermediate Susceptibility or Resistant to Gatifloxacin
(mITT population)

			Susceptibility and MIC (µg/mL) to Antibiotic			
Organism	Patient	Day	Gatifloxacin	Ciprofloxacin	Levofloxacin	Ofloxacin
Gatifloxacin Patients (N =1)						
Staphylococcus epidermidis	125-1048	3	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Placebo Patients (N =5)						
Staphylococcus epidermidis	103-1317	6	Resistant 64	Resistant >4	Resistant >8	Resistant 8
Staphylococcus epidermidis	108-1061	3	Intermediate 4	Susceptible 0.25	Susceptible 0.25	Susceptible 0.5
Staphylococcus epidermidis	121-1392	3	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Staphylococcus haemolyticus	125-1076	3	Intermediate 4	Resistant >4	Resistant 8	Resistant 16
Staphylococcus haemolyticus	131-1312	1	Intermediate 4	Resistant >4	Resistant >8	Resistant >16

TABLE 14 shows the MIC values for the most frequently seen organisms in the mITT population.

TABLE 14
Minimum Inhibitory Concentrations (µg/mL) to Gatifloxacin
(mITT population)

Organism	Gatifloxacin Patients			Placebo Patients		
Visit	N	minimum	maximum	N	minimum	maximum
Haemophilus influenzae						
Day 1	16	0.008	0.06	17	0.008	0.06
Day 6	0	—	—	3	0.015	0.015
Staphylococcus aureus						
Day 1	19	0.06	0.25	10	0.06	0.12
Day 6	3	0.06	0.25	5	0.06	0.25
Staphylococcus epidermidis						
Day 1	13	0.12	2.0	23	0.12	2.0
Day 6	5	0.06	2.0	13	0.12	64.0
Streptococcus mitis						
Day 1	9	0.25	0.5	3	0.5	0.5
Day 6	2	0.25	0.5	0	---	---
Streptococcus oralis						
Day 1	3	0.5	0.5	6	0.5	1.0
Day 6	1	0.5	0.5	1	0.25	0.25
Streptococcus pneumoniae						
Day 1	11	0.06	0.25	10	0.12	0.5
Day 6	1	0.25	0.25	7	0.12	0.5

For all organisms in the mITT population, MICs to gatifloxacin ranged from 0.008 to 64 µg/mL in gatifloxacin patients and from 0.002 to 64 µg/mL in placebo patients. The maximum MIC in both gatifloxacin and placebo patients was for *Staphylococcus epidermidis*. Treatment with gatifloxacin did not lead to an increase in MICs.

STUDY SPCL-GFLX 3/02

A total of 459 patients were enrolled in study 3/02: 230 patients in the gatifloxacin group and 229 in the placebo group. TABLE 15 shows the patient disposition for this study.

TABLE 15
Patient Disposition (study 3/02)

Analysis Population Disposition	Gatifloxacin	Ofloxacin
Safety Population	230	229
Completed	220 (95.7%)	215 (93.9%)
Discontinued	10 (4.3%)	14 (6.1%)
Lost to follow-up	5 (2.2%)	6 (2.6%)
Adverse event	3 (1.3%)	6 (2.6%)
Protocol violation	1 (0.4%)	0
Did not meet inclusion criteria	1 (0.4%)	0
Other	0	2 (0.9%)
Per Protocol Population	78	69
Modified ITT Population	220	222

There were 312 patients excluded from the per protocol (PP) population for one or more of the following reasons:

- 52.6% (121/230) of gatifloxacin patients and 55.0% (126/229) of ofloxacin patients were not culture positive at baseline
- 21.7% (50/230) of gatifloxacin patients and 20.1% (46/229) of ofloxacin patients did not have a day 6 visit with a culture sample that was 12 to 24 hours after their last dose of study medication
- 3.9% (9/230) of gatifloxacin patients and 5.7% (13/229) of ofloxacin patients did not receive the full course of therapy
- 2.6% (6/230) of gatifloxacin patients and 1.3% (3/229) of ofloxacin patients received prohibited concomitant medications during the study
- 1.7% (4/230) of gatifloxacin patients and 0.9% (2/229) of ofloxacin patients had no source documentation
- 0.4% (1/230) of gatifloxacin patients and 0.4% (1/229) of ofloxacin patients had an average ophthalmic sign score <2 at baseline
- 0.4 % (1/230) gatifloxacin patients and 0 ofloxacin patients sensitivity to test drugs was not recorded at baseline

- 16 patients were potentially misrandomized: 11 patients could not document the intended randomized treatment; 2 patients received gatifloxacin who had been randomized to ofloxacin; 3 patients received ofloxacin who had been randomized to gatifloxacin

There were 17 patients who were excluded from the mITT population: 1.3% (3/230) of gatifloxacin patients and 1.3% (3/229) of ofloxacin patients had no postbaseline efficacy assessments and 2.4% (11/459) patients had no documentation as to their intended randomization treatment. The remaining five patients who had been misrandomized were included in the mITT population and analyzed according to their intended treatment.

TABLE 16 gives a summary of the microbiological results in the per protocol (PP) population.

TABLE 16
Summary of Microbiological Cure
(Per Protocol Population)

Microbiological Cure[a]	Gatifloxacin N = 78	Ofloxacin N = 69
Day 3	N = 73	N = 66
Success	60 (82.2%)	53 (80.3%)
Failure	13 (17.8%)	13 (19.7%)
Day 6	N = 78	N = 68
Success	65 (83.3%)	58 (85.3%)
Failure	13 (16.7%)	10 (14.7%)

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

At day 3, of the 13 gatifloxacin patients who failed, 4 patients showed microbial reduction and 9 persistence. Of the 13 ofloxacin patients who failed, 3 patients showed microbial reduction, 7 persistence, and 3 proliferation. At day 6, of the 13 gatifloxacin patients who failed, 4 patients showed microbial reduction, 6 persistence, and 3 proliferation. Of the 10 ofloxacin patients who failed, 3 patients showed reduction, 4 persistence, and 3 proliferation.

Microbiological cure was seen by day 3 for both gatifloxacin and ofloxacin, with success rates of 82.2% and 80.3%, respectively. At day 6 the cure rates were 83.3% and 85.3%, respectively. TABLE 17 shows the eradication rates by organism in the per protocol population.

TABLE 17
Microbiological Response by Bacterial Classification
(Per Protocol Population)

Organism	Day	Gatifloxacin		Ofloxacin	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
All Organisms	3	92	79 (85.9%)	87	72 (82.8%)
	6	98	85 (86.7%)	88	78 (88.6%)
Gram Positive Bacteria	3	63	52 (82.5%)	69	54 (78.3%)
	6	66	54 (81.8%)	67	58 (86.6%)
Gram Negative Bacteria	3	29	27 (93.1%)	18	18 (100.0%)
	6	32	31 (96.9%)	21	20 (95.2%)
Aerococcus viridans	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Corynebacterium pseudodiphtheriticum	3	1	1 (100.0%)	1	1 (100.0%)
	6	1	1 (100.0%)	1	1 (100.0%)
Corynebacterium propinquum	3	4	4 (100.0%)	0	
	6	4	4 (100.0%)	0	
Corynebacterium species	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Enterobacter cloacae	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Enterococcus faecalis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Escherichia coli	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Gemella haemolysans	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Gemella species	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)		
Haemophilus influenzae	3	23	22 (95.7%)	12	12 (100.0%)
	6	26	25 (96.2%)	14	14 (100.0%)
Klebsiella oxytoca	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Moraxella catarrhalis	3	2	2 (100.0%)	0	
	6	2	2 (100.0%)	0	
Morganella morganii	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Neisseria sicca	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Pseudomonas aeruginosa	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Serratia marcescens	3	0		3	3 (100.0%)
	6	0		4	3 (75.0%)
Serratia rubidaea	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	

TABLE 17 (continued)
Microbiological Response by Bacterial Classification
(Per Protocol Population)

Organism	Day	Gatifloxacin		Ofloxacin	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
Staphylococcus aureus	3	8	7 (87.5%)	15	8 (53.3%)
	6	9	9 (100.0%)	14	11 (78.6%)
Staphylococcus capitis	3	2	2 (100.0%)	2	1 (50.0%)
	6	2	2 (100.0%)	2	2 (100.0%)
Staphylococcus epidermidis	3	17	11 (64.7%)	20	15 (75.0%)
	6	17	12 (70.6%)	19	16 (84.2%)
Staphylococcus hominis	3	1	1 (100.0%)	3	3 (100.0%)
	6	1	1 (100.0%)	3	3 (100.0%)
Staphylococcus warneri	3	1	1 (100.0%)	0	
	6	1	0 (0.0%)	0	
Stomatococcus mucilaginosus	3	2	2 (100.0%)	0	
	6	2	2 (100.0%)	0	
Streptococcus intermedius	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Streptococcus mitis	3	1	1 (100.0%)	3	3 (100.0%)
	6	1	1 (100.0%)	3	3 (100.0%)
Streptococcus oralis	3	2	2 (100.0%)	0	
	6	2	2 (100.0%)	0	
Streptococcus pneumoniae	3	18	14 (77.8%)	19	17 (89.5%)
	6	20	14 (70.0%)	19	16 (84.2%)
Streptococcus salivarius	3	1	1 (100.0%)	1	1 (100.0%)
	6	1	1 (100.0%)	1	1 (100.0%)
Streptococcus sanguis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Viridans *streptococcus*	3	1	1 (100.0%)	2	2 (100.0%)
	6	1	1 (100.0%)	2	2 (100.0%)

The eradication rates were similar with gatifloxacin and ofloxacin for both Gram positive and Gram negative bacteria. Ofloxacin was slightly better against *Staphylococcus epidermidis* and *Streptococcus pneumoniae*, but gatifloxacin was better against *Staphylococcus aureus.*

In the per protocol (PP) population the organisms that occurred greater than five times and were treated with gatifloxacin were *Haemophilus influenzae* (25/26 eradicated), *Staphylococcus aureus* (9/9 eradicated), *Staphylocccus epidermidis* (12/17 eradicated), and *Streptococcus pneumoniae* (14/20 eradicated).

TABLE 18 gives a summary of the microbiological results in the modified intent-to-treat (mITT) population.

TABLE 18
Summary of Microbiological Cure
(mITT Population)

Microbiological Cure[a]	Gatifloxacin N = 220	Ofloxacin N = 222
Day 3	N = 98	N = 99
Success	81 (82.7%)	79 (79.8%)
Failure	17 (17.3%)	20 (20.2%)
Day 6	N = 103	N = 100
Success	86 (83.5%)	81 (81.0%)
Failure	17 (16.5%)	19 (19.0%)

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

Microbiological cure with gatifloxacin and ofloxacin were about equal for both groups. Microbiological eradication was evident for both groups by day 3.

TABLE 19 shows the eradication rates by organism in the mITT population.

TABLE 19
Microbiological Response by Bacterial Classification
(mITT Population)

Organism	Day	Gatifloxacin		Ofloxacin	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
All Organisms	3	124	107 (86.3%)	139	116 (83.5%)
	6	131	114 (87.0%)	140	120 (85.7%)
Gram Positive Bacteria	3	85	70 (82.4%)	104	82 (78.8%)
	6	91	75 (82.4%)	104	86 (82.7%)
Gram Negative Bacteria	3	39	37 (94.9%)	35	34 (97.1%)
	6	40	39 (97.5%)	36	34 (94.4%)
Aerococcus viridans	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Corynebacterium pseudodiphtheriticum	3	1	1 (100.0%)	2	1 (50.0%)
	6	1	1 (100.0%)	2	1 (50.0%)
Corynebacterium propinquum	3	4	4 (100.0%)	0	
	6	4	4 (100.0%)	0	
Corynebacterium species	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Enterobacter cloacae	3	0		2	2 (100.0%)
	6	0		2	2 (100.0%)
Enterococcus faecalis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Enterococcus faecium	3	0		0	
	6	1	1 (100.0%)	0	
Escherichia coli	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Gemella haemolysans	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Gemella species	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Haemophilus influenzae	3	31	30 (96.8%)	24	24 (100.0%)
	6	32	31 (96.9%)	25	24 (96.0%)
Haemophilus parainfluenzae	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Klebsiella oxytoca	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Micrococcus species	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Moraxella catarrhalis	3	2	2 (100.0%)	0	
	6	2	2 (100.0%)	0	
Morganella morganii	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Neisseria meningitidis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Neisseria sicca	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Pasteurella haemolytica	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Pseudomonas aeruginosa	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Serratia marcescens	3	0		6	5 (83.3%)
	6	0		6	5 (83.3%)
Serratia rubidaea	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	

TABLE 19 (continued)
Microbiological Response by Bacterial Classification
(mITT Population)

Organism	Day	Gatifloxacin		Ofloxacin	
		Total No.	No. Eradicated (%)	Total No.	No. Eradicated (%)
Staphylococcus aureus	3	17	16 (94.1%)	21	14 (66.7%)
	6	18	18 (100.0%)	21	18 (85.7%)
Staphylococcus capitis	3	2	2 (100.0%)	4	3 (75.0%)
	6	3	3 (100.0%)	4	4 (100.0%)
Staphylococcus epidermidis	3	22	13 (59.1%)	30	21 (70.0%)
	6	23	14 (60.9%)	30	21 (70.0%)
Staphylococcus hominis	3	1	1 (100.0%)	3	3 (100.0%)
	6	1	1 (100.0%)	3	3 (100.0%)
Staphylococcus lugdunensis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Staphylococcus simulans	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Staphylococcus warneri	3	1	1 (100.0%)	0	
	6	1	0 (0.0%)	0	
Stomatococcus mucilaginosus	3	2	2 (100.0%)	1	1 (100.0%)
	6	2	2 (100.0%)	1	1 (100.0%)
Streptococcus intermedius	3	1	1 (100.0%)	1	1 (100.0%)
	6	1	1 (100.0%)	1	1 (100.0%)
Streptococcus mitis	3	2	2 (100.0%)	6	6 (100.0%)
	6	2	2 (100.0%)	2	6 (100.0%)
Streptococcus oralis	3	2	2 (100.0%)	2	2 (100.0%)
	6	2	2 (100.0%)	2	2 (100.0%)
Streptococcus parasanguis	3	0		1	1 (100.0%)
	6	0		1	1 (100.0%)
Streptococcus pneumoniae	3	24	19 (79.2%)	25	21 (84.0%)
	6	26	20 (76.9%)	25	20 (80.0%)
Streptococcus salivarius	3	1	1 (100.0%)	1	1 (100.0%)
	6	1	1 (100.0%)	1	1 (100.0%)
Streptococcus sanguis	3	1	1 (100.0%)	0	
	6	1	1 (100.0%)	0	
Viridans *Streptococcus*	3	1	1 (100.0%)	2	2 (100.0%)
	6	1	1 (100.0%)	2	2 (100.0%)

It appears that for most species the eradication rate was basically equivalent for both gatifloxacin and ofloxacin.

In the intent-to-treat (mITT) population the organisms that occurred greater than five times and were treated with gatifloxacin were *Haemophilus influenzae* (31/32 eradicated), *Staphylococcus aureus* (18/18 eradicated), *Staphylococcus epidermidis* (14/23 eradicated), and *Streptococcus pneumoniae* (20/26 eradicated).

For all organisms isolated from gatifloxacin patients in the mITT population at baseline which had MICs determined and for which interpretive criteria have been established, 94.0% (109/116) were susceptible to gatifloxacin (6.0% not susceptible). There were 13.7% (13/95), 9.8% (13/132), and 11.8% (14/119) of these organisms that were not susceptible to ciprofloxacin, levofloxacin, and ofloxacin, respectively. At the end of treatment (Day 6 visit) 86.4% (19/22) of the organisms that were not eradicated were susceptible to gatifloxacin (13.6% not susceptible). There were 50.0% (6/12), 25.0% (6/24), and 35.0% (7/20) of these organisms that were not susceptible to ciprofloxacin, levofloxacin, and ofloxacin, respectively.

For all organisms isolated from ofloxacin patients in the mITT population at baseline which had MICs determined and for which interpretive criteria have been established, 93.4% (114/122) were susceptible to gatifloxacin (6.4% not susceptible). There were 13.2% (13/98), 9.5% (13/137), and 12.3% (15/122) of these organisms were not susceptible to ciprofloxacin, levofloxacin, and ofloxacin, respectively. Approximately 7-13% of the pathogens were, therefore, not susceptible to fluoroquinolones. Approximately 2-6% of the pathogens were susceptible to gatifloxacin but not the other fluoroquinolones. At the end of treatment (Day 6 visit) 86.4% (19/22) organisms that were not eradicated were susceptible to gatifloxacin, 73.7% (14/19) to ciprofloxacin, 83.9% (26/31) to levofloxacin, and 79.2% (19/24) to ofloxacin.

TABLE 20 summarizes the MIC data for the isolates in the mITT population that were not susceptible to gatifloxacin. Several organisms isolated from the same patient on the same or different days are included.

TABLE 20
Organisms with Intermediate Susceptibility or Resistant to Gatifloxacin
(mITT population)

			Susceptibility and MIC (µg/mL) to Antibiotic			
Organism	Patient	Day	Gatifloxacin	Ciprofloxacin	Levofloxacin	Ofloxacin
Gatifloxacin Patients (N =10)						
Staphylococcus simulans	204-2161	1	Intermediate 4	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus	204-2202	1	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis	204-2247	1	Resistant 32	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis	217-2070	6	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis	212-2221	6	Resistant 32	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis	225-2405	3	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Staphylococcus haemolyticus	223-2016	3	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus		1	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis	225-2305	3	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Staphylococcus haemolyticus		3	Intermediate 4	Resistant >4	Resistant >8	Resistant 16
Staphylococcus aureus	242-2097	1	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus		3	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus capitis	244-2282	1	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis		1	Intermediate 4	Resistant >4	Resistant 8	Resistant 16
Stapylococcus epidermidis		6	Resistant 8	Resistant >4	Resistant >8	Resistant >16

TABLE 20 (continued)
Organisms with Intermediate Susceptibility or Resistant to Gatifloxacin
(mITT population)

			Susceptibility and MIC (µg/mL) to Antibiotic			
Organism	Patient	Day	Gatifloxacin	Ciprofloxacin	Levofloxacin	Ofloxacin
Ofloxacin Patients (N =9)						
Staphylococcus aureus	201-2040	1	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus		3	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus	204-2093	1	Intermediate 4	Resistant >4	Resistant 8	Resistant 8
Staphylococcus epidermidis		1	Intermediate 4	Resistant >4	Resistant 8	Resistant 16
Staphylococcus simulans	204-2115	1	Resistant 16	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis	214-2028	1	Resistant 128	Resistant >4	Resistant >8	Resistant >16
Staphylococcus capitis	244-2128	3	Intermediate 4	Resistant >4	Resistant >8	Resistant >16
Staphylococcus capitis		6	Resistant 32	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus	224-2298	1	Resistant 64	Resistant >4	Resistant >8	Resistant .>16
Staphylococcus aureus		6	Resistant 64	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus		3	Resistant 64	Resistant >4	Resistant >8	Resistant 16
Staphylococcus aureus	225-2222	1	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus aureus		3	Resistant 8	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis	244-2509	3	Intermediate 4	Resistant >4	Resistant >8	Resistant >16
Staphylococcus epidermidis		6	Intermediate 4	Resistant >4	Resistant >8	Resistant >16
Stapylococcus hominis	254-2553	1	Intermediate 4	Resistant >4	Resistant >8	Resistant >16

There were 31 isolates from 19 patients (10 gatifloxacin and 9 ofloxacin) in the mITT population that were not susceptible to gatifloxacin: 1 intermediate and 11 resistant *Staphylococcus aureus*, 1 intermediate and 2 resistant *Staphylococcus capitis*, 4 intermediate and 7 resistant *Staphylococcus epidermidis*, 1 intermediate and 1 resistant *Staphylococcus haemolyticus*, 1 intermediate *Staphylococcus hominis*, and 1 intermediate and 1 resistant *Staphylococcus simulans*.

There were 60 isolates from 39 patients (22 gatifloxacin and 17 ofloxacin) in the mITT population that were not susceptible to ofloxacin: 1 resistant *Pseudomonas aeruginosa*, 1 intermediate *Rosemonas* species. 13 resistant *Staphylococcus aureus*, 4 resistant *Staphylococcus capitis*, 3 intermediate and 26 resistant *Staphylococcus epidermidis*, 2 resistant *Staphylococcus haemolyticus*, 1 resistant *Staphylococcus hominis*, 2 resistant *Staphylococcus simulans*, and 7 intermediate *Streptococcus pneumoniae*.

Clinical and/or microbiological success was achieved for many of these patients given either gatifloxacin or ofloxacin treatment, despite *in vitro* resistance.

TABLE 21 shows the MIC values for the most frequently seen organisms in the mITT population.

TABLE 21
Minimum Inhibitory Concentrations (µg/mL) to Gatifloxacin
(mITT population)

Organism	Gatilfoxacin Patients			Ofloxacin Patients		
Visit	N	minimum	Maximum	N	minimum	maximum
Haemophilus influenzae						
Day 1	33			25		
Day 6	1			2		
Staphylococcus aureus						
Day 1	19			22		
Day 6	1			4		
Staphylococcus capitis						
Day1	3			6		
Day 6	0			1		
Staphylococcus epidermidis						
Day 1	24			31		
Day 6	8			7		
Streptococcus mitis						
Day 1	2			6		
Day 6	0			1		
Streptococcus pneumoniae						
Day 1	26			25		
Day 6	7			5		

For all organisms in the mITT population, MICs to gatifloxacin ranged from ~ ~ in the gatifloxacin group and from ~ ~ . in the ofloxacin group. The maximum MIC in both gatifloxacin and ofloxacin groups was for *Staphylococcus epidermidis*. Treatment with gatifloxacin did not lead to an increase in MICs.

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