

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22548Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

16 April 2010

**NDA:** 22-548/N-000

**Drug Product Name**

**Proprietary:**

ZYMAXID™ 0.5%

**Non-proprietary:**

gatifloxacin ophthalmic solution, 0.5%

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
07/30/09	07/30/09	8/11/09	8/13/09
01/08/10	01/11/10	n/a	n/a
03/26/10	03/26/10	n/a	n/a

**Submission History (for amendments only): N/A**

**Applicant/Sponsor**

**Name:**

Allergan, Inc.

**Address:**

2525 Dupont Drive

Irvine CA 92612

**Representative:**

Joanne Lemmo

Sr. Manager, Regulatory Affairs

**Telephone:**

714-246-5844

**Name of Reviewer:**

Robert J. Mello, Ph.D.

**Conclusion:**

The application is recommended for approval from microbiology product quality standpoint.

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## Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original NDA, 505(b)(1)
  - 2. SUBMISSION PROVIDES FOR:** U.S. Marketing Authorization
  - 3. MANUFACTURING SITE:** Allergan Sales, LLC, Inc.  
8301 Mars Drive  
Waco, TX 76712
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Topical, ophthalmic solution, sterile, 0.5% packaged in multiple-dose dropper bottles in the following fill volume/bottle capacity configurations: 1 mL/5-mL, 2.5 mL/5-mL, (b) (4)
  - 5. METHOD(S) OF STERILIZATION:** (b) (4)
  - 6. PHARMACOLOGICAL CATEGORY:** Antibiotic – treatment of bacterial conjunctivitis
- B. SUPPORTING/RELATED DOCUMENTS:**
- Microbiology review #1 for NDA 19-700/SCP-023, Lead Supplement, dated 19 September 2002 (S. Langille).
- C. REMARKS:**
- There was no ONDQA Initial Quality Assessment on file in DARRTS.
  - The submission was provided in electronic (eCTD) format accessible via the Global Submit Review system.

**filename:** N22548N000R1.doc

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability – Recommend Approval**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The drug product is an aqueous formulation containing benzalkonium chloride as a (b) (4). The drug product is formulated, (b) (4). Component plastic 5ml bottles and dropper tips are sterilized by (b) (4). (b) (4) Caps are (b) (4). (b) (4) The drug product is (b) (4) to fill volumes of either 1ml, 2.5ml or (b) (4).
- B. Brief Description of Microbiology Deficiencies - None**
- C. Assessment of Risk Due to Microbiology Deficiencies – N/A**

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Robert J. Mello, Ph.D.  
Senior Microbiology Reviewer
- B. Endorsement Block** \_\_\_\_\_  
John W. Metcalfe, Ph.D.  
Senior Microbiology Reviewer
- C. CC Block**  
NDA 22-548 DARRTS file

17 pages 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%

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

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/s/

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ROBERT J MELLO  
04/16/2010

JOHN W METCALFE  
04/16/2010  
I concur.

## Division of Anti-Infective and Ophthalmology Products Clinical Microbiology Review

**NDA: 022548**

Date Company Submitted: 20 August 2009  
Date Assigned: 24 August 2009  
Date Completed: 24 February 2010  
Reviewer: Kerry Snow MS

**NAME AND ADDRESS OF APPLICANT:**

Allergan, Inc.  
2525 Dupont Drive  
Irvine, CA 92612

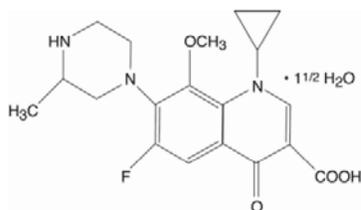
**CONTACT PERSON:**

Joanne Lemmo, Sr. Manager, Regulatory Affairs  
(714) 246-5844

**DRUG PRODUCT NAMES:**

Established Name: Gatifloxacin  
Proposed Trade Name: ZYMAXID™  
Chemical Name: (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sesquihydrate

**STRUCTURAL FORMULA:**



**MOLECULAR FORMULA:** C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> · 1½H<sub>2</sub>O

**MOLECULAR WEIGHT:** 402.42

**DRUG CATEGORY:**

Antimicrobial

**PROPOSED DOSAGE FORM AND STRENGTH:**

5 mL bottle containing 2.5 mL (b) (4) gatifloxacin ophthalmic solution 0.5% (5 mg/mL)

**ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:**

Day 1: Instill one drop every two hours in affected eye(s) while awake, up to 8 times.  
Days 2 through (b) (4) Instill one drop two times daily in the affected eye(s) while awake,  
(b) (4)

**DISPENSED:**

Rx

**PROPOSED INDICATION:**

Treatment of bacterial conjunctivitis

**RELATED DOCUMENTS:**

IND 59408, Gatifloxacin ophthalmic solution  
NDA 21493, Zymar (gatifloxacin ophthalmic solution) 0.3%

**TYPE OF SUBMISSION:**

New Drug Application

**PURPOSE OF SUBMISSION:**

This New Drug Application (NDA) is submitted to seek approval for the use of gatifloxacin ophthalmic solution 0.5% for the treatment of bacterial conjunctivitis in adults and pediatric patients one year or older. This review addresses the microbiologic efficacy of gatifloxacin ophthalmic solution 0.5% as a topical antibacterial. Supportive data, reviewed here, include in vitro antibacterial activity of gatifloxacin against bacterial isolates recovered in two pivotal studies and clinical efficacy of gatifloxacin, compared to vehicle.

**REMARKS:**

The Applicant has referenced NDA 21-493 for information regarding nonclinical pharmacology, pharmacokinetics, and toxicology. New data in this submission include the results of one nonclinical pharmacokinetic study of the ocular pharmacokinetics of gatifloxacin ophthalmic solution in Dutch-Belted rabbits (0.3% QID versus 0.5% BID), and two identically-designed phase 3 multi-center clinical studies (Study 198782-004, performed in the United States, and Study 198782-005, performed in India).

**SUMMARY AND RECOMMENDATIONS:**

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), (b) (4) (b) (4) 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.

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## EXECUTIVE SUMMARY

### I. IN VITRO INFORMATION

#### MECHANISM OF ACTION

The 4-quinolones act by disrupting two bacterial enzymes, DNA gyrase and DNA topoisomerase IV (both categorized as type 2 topoisomerases). The Applicant has provided no data or summary information in this submission, from studies designed to investigate the mechanism of action of gatifloxacin.

#### ANTIMICROBIAL SPECTRUM OF ACTIVITY

Recent studies suggest that gatifloxacin is active against bacteria commonly associated with conjunctivitis, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, staphylococci, *Corynebacterium* species, and *Streptococcus viridans* group, including isolates with reduced susceptibility to first-generation fluoroquinolones (e.g. ciprofloxacin). The Applicant has included no new data in this submission, other than that collected in the two Phase 3 trials, regarding the in vitro antibacterial activity of gatifloxacin.

#### RESISTANCE STUDIES

Chromosomal mutations account for the majority of currently described quinolone resistance mechanisms. Fourth-generation fluoroquinolones may have activity against isolates with reduced susceptibility to other fluoroquinolones (e.g. ciprofloxacin). Recent studies have suggested increased resistance to fluoroquinolones, including fourth-generation fluoroquinolones in some *Corynebacterium* species and in *Staphylococcus epidermidis*. The Applicant has provided no new data in this submission regarding the development of resistance in ophthalmic bacterial pathogens to gatifloxacin.

### II. HUMAN AND ANIMAL STUDIES

#### ANIMAL DISEASE MODELS

Pharmacokinetic studies in Dutch-Belted rabbits suggest that gatifloxacin exposure, expressed as  $AUC_{0-12hr}$  (ng·h/g) in tears is comparable in ZYMAR® and 0.5% Gatifloxacin Ophthalmic Formulation, and is in excess of the MICs of most pathogens commonly associated with conjunctival bacterial infections. Mean tear concentrations of gatifloxacin at 6 and 12 hours, following administration 0.5% Gatifloxacin Ophthalmic Formulation, also exceed the MICs for common ophthalmic pathogens. The Applicant has included no new data in this submission, from studies of gatifloxacin efficacy against ophthalmic pathogens in animal models.

#### PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The Applicant has provided no new data in this submission, regarding the pharmacokinetic/pharmacodynamic behavior of gatifloxacin 0.5% ophthalmic solution in humans.

### III. CLINICAL TRIALS

The Applicant has submitted data from two Phase 3 clinical trials, designed to demonstrate the efficacy and safety of gatifloxacin ophthalmic solution 0.5%, compared to placebo, in the treatment of acute bacterial conjunctivitis in subjects  $\geq 1$  year of age, as measured by clinical success at Day 6 (5 days of dosing, followed by an exit visit). The trial designs were identical and were titled, "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 004 was conducted solely in the U.S. (578 subjects enrolled) and Study 005 conducted primarily in India (770 subjects enrolled at 29 sites in India, 89 subjects enrolled at 10 sites in the U.S.).

Significant differences in the studies included the age of subjects seen, with subjects enrolled in Study 005 approximately 10 years older than subjects enrolled in Study 004, and demographics (with the majority of subjects in Study 005 being Asian, while the majority of subjects in Study 004 Caucasian). Differences also included the variety of principle pathogens seen in the two studies. Specific pathogens commonly associated with bacterial conjunctivitis, including *H. influenzae* and *S. pneumoniae*, were not isolated from in subjects seen by investigators at Indian sites, while pathogens uncommonly associated with bacterial conjunctivitis diagnosed in the U.S. (including coliform bacteria, *P. aeruginosa*, and *Acinetobacter* species) were isolated from subjects seen at Indian sites, but rarely or never from subjects seen at U.S. sites. Gatifloxacin susceptibility results for principle pathogens listed in summary tables were generally higher against isolates recovered from specimens collected in Subject 005, compared to isolates from Study 004. There was higher baseline severity of mucopurulent discharge noted in subjects in Study 005, compared to Study 004.

Using the up to Day 6 analysis method (mITT population, pooled data), clinical success in the gatifloxacin treatment group was 58.0% and clinical success in the vehicle treatment group was 45.5% ( $p = 0.001$ ). Clinical success in Study 004 (mITT population) was demonstrated in 64.1% of subjects in the gatifloxacin arm, compared to 50.0% in the vehicle arm ( $p = 0.010$ ). In Study 005 (mITT population), clinical success was demonstrated in 51.5% of subjects in the gatifloxacin arm, compared to 41.3% of subjects in the vehicle arm ( $p = 0.055$ ).

Data collected in Studies 004 and 005, analyzed separately and as pooled data, support the inclusion of *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus pneumoniae*, *S. mitis* group, *S. oralis*, and *H. influenzae* in the proposed label for ZYMAXID™. Each of these species has been associated with bacterial conjunctivitis in the current literature, and each was isolated in quantities above the established threshold levels discussed at IND discussions prior to this Application. Each was associated with adequate microbiological cure based on the number of isolates seen, e.g. 5-9 isolates with  $\geq 80\%$  eradication or  $\geq 10$  isolates with  $\geq 50\%$  eradication. Although no information regarding the in vitro activity of gatifloxacin against recent isolates of ocular pathogens was submitted in this NDA (other than data from the two Phase 3 clinical trials), and the MIC<sub>90</sub> of gatifloxacin against certain pathogens (notably *S. aureus*) exceeded current CLSI susceptibility breakpoints, exposure to the antimicrobial is expected to far exceed breakpoint levels. Inclusion of (b) (4) (b) (4) (b) (4) in the proposed label for ZYMAXID™ is not supported by the data included in this Application. No isolates of these ocular pathogens were recovered from gatifloxacin-treated subjects seen in the U.S.

2 pages have been withheld in full as B(4) CCI/TS draft labeling immediately following this page.

## INTRODUCTION

### BACTERIAL CONJUNCTIVITIS

Microbial conjunctivitis may be caused by a wide variety of pathogens, including viruses, bacteria, parasites, and fungi. Many microorganisms considered to be potential conjunctival pathogens are routinely present in the healthy eye, including *Staphylococcus epidermidis*, *Corynebacterium* species and *Propionibacterium acnes* [Graham 2007]. Viral etiology is probably the most common form of acute conjunctivitis, with the majority of cases caused by adenoviruses. Bacterial conjunctivitis is frequently associated with a compromised conjunctival epithelium [Mandell 2005], and is most commonly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*.

Laboratory identification of the etiologic agents associated with cases of conjunctivitis is rarely performed. Diagnosis is usually performed by the patient, and differential diagnosis (differentiating bacterial etiology from viral etiology) is marginally significant. Most cases are self-resolving, with symptoms disappearing before bacterial culture results would be available.

There is a high rate of cure in cases of acute bacterial conjunctivitis when no treatment is given (65% within 2-5 days) [Rose 2007]. Recent meta-analysis studies have shown, however, that antibiotic treatment is associated with improved rates of clinical remission, and early and late microbiological remission [Sheikh 2001].

Treatment, if given, usually involves topical administration of a broad-spectrum antibiotic. Aminoglycosides, fluoroquinolones, and sulfacetamide are frequently prescribed as first-line agents. If antibacterials are prescribed, treatment should be guided by laboratory findings. Appropriate procedures for laboratory diagnosis of bacterial conjunctivitis include a conjunctival scraping for culture and Gram stain (and/or Giemsa stain), taken with a calcium alginate swab. Inoculation media should include blood and chocolate agar, and a fungal growth medium.

### FLUOROQUINOLONE CLASS OF ANTIBIOTICS

The fluoroquinolones are concentration-dependent bactericidal antimicrobials that act by disrupting the bacterial enzymes DNA gyrase and topoisomerase IV. The fluoroquinolone class is considered "broad spectrum", but activity against specific pathogens is structure-related, with particular substituent groups providing enhanced coverage against certain bacteria [Bryskier 2005]. Fourth generation fluoroquinolones (e.g. gatifloxacin and moxifloxacin, both possessing a C-OCH<sub>3</sub> group at position 8) have increased activity against Gram positive pathogens and fluoroquinolone-resistant isolates [Scoper 2008], including isolates resistant to other fluoroquinolones [Park 2009].

Topical fluoroquinolones for ophthalmic indications have been used since 1990, when ciprofloxacin hydrochloride (ophthalmic drops) was approved (Ciloxan; NDA 019992). Fluoroquinolones currently marketed for ophthalmic infections (conjunctivitis and/or corneal ulcers) include ciprofloxacin (Ciloxan solution and ointment), gatifloxacin (Zymar), levofloxacin (Quixin and Iquix), moxifloxacin (Vigamox), ofloxacin (Ocuflax), and besifloxacin (Besivance).

ZYMAR® (gatifloxacin ophthalmic solution) 0.3% was approved in March 2003 under NDA 21,493. The Applicant (Allergan, Inc.) has reformulated gatifloxacin ophthalmic solution at a higher dosage strength (0.5%), with the goal of achieving reduced dosing frequency (twice daily, compared to four times daily for ZYMAR®) and greater bacterial killing. The Applicant contends that the new formulation, with reduced dosing frequency, will result in greater efficacy, greater compliance, and fewer adverse events, compared to the 0.3% formulation. In addition to the

increased dosage strength (0.5% gatifloxacin, compared to 0.3%), the new formulation also includes a slightly lower sodium chloride concentration and a reduction in pH, compared to Zymar<sup>®</sup>. All other elements of the formulations are identical, including excipients.

## **IN VITRO INFORMATION**

### **MECHANISM OF ACTION**

The 4-quinolones act by disrupting two bacterial enzymes, DNA gyrase and DNA topoisomerase IV (both categorized as type 2 topoisomerases). DNA gyrase is responsible for introducing negative supercoils into bacterial DNA. Topoisomerase IV (a homolog of DNA gyrase) is responsible for decatenation of DNA following replication to allow integration into daughter cells. Both enzymes are composed of two groups of two identical subunits (A and B subunits in DNA gyrase, and their homolog C and E subunits in topoisomerase IV). Specific quinolones may have greater affinity for a particular enzyme or subunit homolog, forming reversible complexes consisting of the antimicrobial, the enzyme, and the bacterial DNA. The bactericidal activity of the 4-quinolones is most likely related to the release of DNA fragments into the cellular matrix [Drlica 1997].

The Applicant has provided no data or summary information in this submission, describing the mechanism of action of gatifloxacin.

### **ANTIMICROBIAL SPECTRUM OF ACTIVITY**

The fourth-generation quinolones (gatifloxacin and moxifloxacin) retain the broad-spectrum antibacterial activity of earlier generations (ciprofloxacin, levofloxacin, etc.), with demonstrated in vitro potency against Gram-negative bacilli (including *Haemophilus* species, *Pseudomonas aeruginosa*, and most members of the family Enterobacteriaceae) and most staphylococci. In addition, gatifloxacin and moxifloxacin have activity against some streptococci, some anaerobes, and some bacteria with reduced susceptibility to earlier generations of fluoroquinolones. The fourth generation fluoroquinolones have also demonstrated greater activity than ciprofloxacin or ofloxacin against staphylococcal isolates [Schlech 2005].

In a 2003 study, investigators compared the in vitro antibacterial activity of gatifloxacin, moxifloxacin, levofloxacin, ciprofloxacin, and ofloxacin against isolates collected from subjects diagnosed with bacterial keratitis [Kowalski 2003]. The E-test method was used to determine in vitro susceptibility, with susceptibility breakpoints based on CLSI documents available at the time (MIC  $\leq$  2 mcg/ml was deemed susceptible for ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin, MIC  $\leq$  1 mcg/ml was deemed susceptible for ciprofloxacin). "Fluoroquinolone resistant" was defined as resistance to both ofloxacin and ciprofloxacin. The results of the study are summarized in Table 1. Against these isolates, gatifloxacin activity was generally less than that of moxifloxacin and generally greater than levofloxacin. Based on MIC<sub>90</sub> values, gatifloxacin was not active against isolates of staphylococci and *Pseudomonas aeruginosa* described as "fluoroquinolone-resistant."

The Applicant has provided no data in this submission, regarding the in vitro spectrum of activity of gatifloxacin against bacterial pathogens associated with ocular disease, other than data collected in the two pivotal trials (discussed later in this review).

**Table 1:** Minimum inhibitory concentrations (MIC) (mcg/ml) for bacterial keratitis isolates to fluoroquinolone antibiotics

	n	Median	MIC90	Mode	Susceptibility
<i>Staphylococcus aureus</i> —Fluoroquinolone susceptible					
Moxifloxacin	25	0.032	0.047	0.032, 0.047	100%
Gatifloxacin	25	0.094	0.22	0.064	100%
Levofloxacin	25	0.19	0.38	0.19	100%
Ciprofloxacin	25	0.38	0.5	0.38	100%
Ofloxacin	25	0.5	0.75	0.5	100%
<i>Staphylococcus aureus</i> —Fluoroquinolone resistant					
Moxifloxacin	25	1.5	4.0	1.0, 1.5	68%
Gatifloxacin	25	4.0	12.0	3.0	8%
Levofloxacin	25	16.0	32.0	16.0, 32.0	0%
Ciprofloxacin	25	64.0	128.0	64.0	0%
Ofloxacin	25	64.0	64.0	64.0	0%
<i>coagulase negative Staphylococcus</i> —Fluoroquinolone susceptible					
Moxifloxacin	10	0.064	0.125	0.064	100%
Gatifloxacin	10	0.125	0.19	0.094	100%
Levofloxacin	10	0.19	0.19	0.19	100%
Ciprofloxacin	10	0.22	0.38	0.19, 0.38	100%
Ofloxacin	10	0.5	0.75	0.38, 0.5	100%
<i>coagulase negative Staphylococcus</i> —Fluoroquinolone resistant					
Moxifloxacin	10	2.5	3.0	3.0	50%
Gatifloxacin	10	3.0	3.0	3.0	40%
Levofloxacin	10	64.0	64.0	64.0	10%
Ciprofloxacin	10	64.0	64.0	64.0	0%
Ofloxacin	10	64.0	64.0	64.0	0%
<i>Streptococcus pneumoniae</i>					
Moxifloxacin	20	0.125	0.19	0.19	100%
Gatifloxacin	20	0.22	0.25	0.25	100%
Levofloxacin	20	0.75	1.0	0.75	95%
Ciprofloxacin	20	0.75	2.0	0.38	85%
Ofloxacin	20	2.0	4.0	1.5, 2.0	70%
<i>Streptococcus viridans</i> group					
Moxifloxacin	20	0.125	0.19	0.19	100%
Gatifloxacin	20	0.25	0.38	0.38	100%
Levofloxacin	20	0.75	1.0	1.00	100%
Ciprofloxacin	20	1.0	4.0	0.25, 0.5, 1.0, 2.0	60%
Ofloxacin	20	2.0	4.0	4.0	55%
<i>Pseudomonas aeruginosa</i> —Fluoroquinolone susceptible					
Moxifloxacin	25	0.5	0.75	0.25, 0.5	100%
Gatifloxacin	25	0.25	0.38	0.19, 0.38	100%
Levofloxacin	25	0.38	0.5	0.25, 0.38	100%
Ciprofloxacin	25	0.094	0.125	0.094	100%
Ofloxacin	25	0.75	1.5	0.5, 1.0	100%
<i>Pseudomonas aeruginosa</i> —Fluoroquinolone resistant are resistant to all generations of fluoroquinolones					
<i>Serratia marcescens</i>					
Moxifloxacin	10	0.25	0.38	0.38	100%
Gatifloxacin	10	0.25	0.38	0.25	100%
Levofloxacin	10	0.19	0.25	0.19	100%
Ciprofloxacin	10	0.064	0.094	0.064	100%
Ofloxacin	10	0.5	0.75	0.5	100%
<i>Haemophilus</i> species					
Moxifloxacin	10	0.039	0.19	0.016, 0.023, 0.19	100%
Gatifloxacin	10	0.017	0.064	0.008	100%
Levofloxacin	10	0.024	0.032	0.016	100%
Ciprofloxacin	10	0.014	0.032	0.012	100%
Ofloxacin	10	0.05	0.125	0.047	100%
<i>Moraxella</i> species					
Moxifloxacin	10	0.047	0.047	0.047	100%
Gatifloxacin	10	0.032	0.032	0.032	100%
Levofloxacin	10	0.047	0.064	0.064	100%
Ciprofloxacin	10	0.032	0.064	0.032	100%
Ofloxacin	10	0.125	0.19	0.125	100%

n = the number of isolates tested; median = the middle MIC value in the ordered array of MIC values; MIC90 = the MIC that inhibits 90% of bacterial isolates tested; mode = the MIC value occurring with the greatest frequency; susceptibility is the cumulative susceptibility of the isolates to the antibiotics based on the NCCLS serum standards.

Source: Kowalski 2003

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*In Summary:*

Recent studies suggest that gatifloxacin is active against bacteria commonly associated with conjunctivitis, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, staphylococci, *Corynebacterium* species, and *Streptococcus viridans* group, including isolates with reduced susceptibility to first-generation fluoroquinolones (e.g. ciprofloxacin). The Applicant has included no data in this submission other than that obtained in the two pivotal studies, regarding the in vitro antibacterial activity of gatifloxacin.

## RESISTANCE STUDIES

Quinolone resistance most frequently occurs by chromosomal mutations in the genes encoding the principle quinolone targets, DNA gyrase (*gyrA* and *gyrB*) and topoisomerase IV (*parC* and *parE*). Additional mechanisms of resistance include the expression of multi-drug efflux pumps [Mazzariol 2000] and the transfer of plasmid-borne resistance determinants, including *qnr* genes, *aac(6')-IB-cr*, and *qepA* [Ma 2008]. Not all members of the fluoroquinolone class are affected by all mechanisms. Quinolones with multiple targets (e.g. gatifloxacin and levofloxacin) are generally less affected by certain chromosomal mutations, and the molecular structure of the specific quinolone may result in dramatic differences in MICs against fluoroquinolone-resistant isolates [Becnel 2008]. Some studies have suggested that unknown resistance mechanisms may be present in a high percentage of quinolone-resistant bacteria [Morgan-Linnell 2008]. Recent investigations of pathogens collected from ocular infections have identified frequent mutations in the quinolone resistance determining region (QRDR) in *Staphylococcus epidermidis* [Yamada 2008] and in specific mutations in the *gyrA* and *parC* genes [Betanzos-Cabrera 2009], while separate investigations have demonstrated high levels of quinolone resistance in *Corynebacterium macginleyi*, a recently recognized ocular pathogen [Eguchi 2008].

The Applicant has included no studies of the development of resistance to gatifloxacin in ocular pathogens.

*In summary:*

Chromosomal mutations account for the majority of currently described quinolone resistance mechanisms. Fourth-generation fluoroquinolones may have activity against isolates with reduced susceptibility to other fluoroquinolones (e.g. ciprofloxacin). Recent studies have suggested increased resistance to fluoroquinolones, including fourth-generation fluoroquinolones in some *Corynebacterium* species and in *Staphylococcus epidermidis*. The Applicant has provided no data in this submission, other than susceptibility testing of isolates collected in the two phase three clinical trials (discussed later in this review), regarding the development of resistance in ophthalmic bacterial pathogens to gatifloxacin.

## HUMAN AND ANIMAL STUDIES

### ANIMAL STUDIES

The Applicant has presented data from investigations designed to compare the pharmacokinetics of 0.3% gatifloxacin ophthalmic solution QID to 0.5% gatifloxacin ophthalmic solution BID in Dutch-Belted rabbits (Report PK-08-P029-BM). The study was conducted by the Applicant in 2008. The dosing regimen for the study is summarized in Table 2.

**Table 2:** Study Group Arrangement and Dosing

Group	Treatment	Frequency	Dose Volume (µL)	N
1	0.3% Gatifloxacin Ophthalmic Formulation (ZYMAR®)	3X/Day – 1 drop each at 0min, 15min, and 30min	35	12F
2	0.5% Gatifloxacin Ophthalmic Formulation	3X/Day – 1 drop each at 0min, 15min, and 30min	35	12F
3	0.3% Gatifloxacin Ophthalmic Formulation (ZYMAR®)	<b>Day 1:</b> 4X/Day – 1 drop each at 0min, 15min, 30min, and 10hr <b>Day 2:</b> 2X/Day – 1 drop each at 0min and 6hr	35	10F
4	0.5% Gatifloxacin Ophthalmic Formulation	<b>Day 1:</b> 4X/Day – 1 drop each at 0min, 15min, 30min, and 10hr <b>Day 2:</b> 1X/Day – 1 drop at 0min	35	12F
5	No Dose	--	--	2F

Group 5 was not dosed and tissues were collected for bioanalytical controls.

F = female

Source: This submission; Table 2.6.4-2

Aqueous humor, conjunctiva, cornea, and tear samples were collected at specified time points and analyzed using validated LC-MS/MS assays. Undosed animals (n = 2) were used as controls. Mean PK parameters for the four specimen types (in Groups 1 and 2) are summarized in Table 3. Gatifloxacin exposure reported as AUC<sub>0-12hr</sub> was generally similar between the two experimental groups. Mean C<sub>max</sub> values for Group 2 (0.5% gatifloxacin) were significantly higher than those obtained for Group 1 (Zymar®) in tear specimens, but comparable for other specimen types. Mean concentrations (C<sub>max</sub> and AUC<sub>0-12hr</sub>) of both treatments exceeded the MIC<sub>90</sub> of most commonly isolated ophthalmic pathogens (see above).

**Table 3:** Mean Pharmacokinetic Parameters of Gatifloxacin in Aqueous Humor, Conjunctiva, Cornea, and Tears Following Administration of 3 Drops of 0.3% Gatifloxacin Ophthalmic Formulation (ZYMAR®, Group 1) or 0.5% Gatifloxacin Ophthalmic Formulation (Group 2) in Dutch-Belted Rabbits

	$C_{max}$ (ng/g) <sup>a</sup>	$T_{max}$ (hr)	$AUC_{0-12hr}$ (ng·hr/g) <sup>b</sup>
Aqueous Humor			
Group 1	1200 ± 700	1.00	3880 ± 780
Group 2	1130 ± 430	1.00	3730 ± 260
Conjunctiva			
Group 1	6430 ± 3950	0.500	7490 ± 1110
Group 2	8340 ± 3630	0.250	7640 ± 1710
Cornea			
Group 1	14000 ± 6000	0.500	41100 ± 4800
Group 2	16300 ± 2800	0.250	43100 ± 3100
Tears			
Group 1	74400 ± 40400	0.250	166000 ± 53000
Group 2	213000 ± 262000	0.250	199000 ± 45000

<sup>a</sup>  $C_{max}$  reported as ng/g except for aqueous humor where  $C_{max}$  is reported as ng/mL

<sup>b</sup>  $AUC_{0-12hr}$  reported as ng·hr/g except for aqueous humor where  $AUC_{0-12hr}$  is reported as ng·hr/mL.

Data presented are mean ± SD for  $C_{max}$ ; mean ± SEM for  $AUC_{0-12hr}$ ; mean values for  $T_{max}$

Treatment Group 1 = Zymar® (0.3% gatifloxacin ophthalmic solution) 3 drops 15 minutes apart;

Treatment Group 2 = 0.5% gatifloxacin ophthalmic solution 3 drops 15 minutes apart.

Mean PK parameters for animals tested in the 2-day protocol (Groups 3 and 4) are summarized in Table 4. The range of values for most measurements was large (with SD approximating the mean in some cases). Gatifloxacin concentrations in the 6-hour (post last dose) samples for the 0.5% formulation were notably less than those taken at the same time point for animals treated with Zymar® (gatifloxacin 0.3%), except for those from aqueous humor specimens, and barely exceeded  $MIC_{90}$  values for some ophthalmic pathogens (described in Table 1), in corneal and conjunctival specimens.

**Table 4:** Mean Gatifloxacin Concentrations in Conjunctiva, Cornea, Aqueous Humor, and Tears Following Administration of 0.3% Gatifloxacin Ophthalmic Formulation (ZYMAR®) or 0.5% Gatifloxacin Ophthalmic Formulation in Dutch-Belted Rabbits

Sampling Time Post Last Dose (hours)	GATIFLOXACIN CONCENTRATION (mean ± SD)			
	Group 3 (ZYMAR® Treatment)			
	Conjunctiva (ng/g)	Cornea (ng/g)	Aqueous Humor (ng/mL)	Tears (ng/g)
0.25	6670 ± 3910	10700 ± 5600	199 ± 92	281000 ± 173000
0.5	3870 ± 2540	8900 ± 3200	331 ± 116	24700 ± 15100
1	1520 ± 570	7380 ± 3220	638 ± 422	55900 ± 39200
2	1660 ± 1270	5830 ± 2350	397 ± 186	205000 ± 243000
6	1090 ± 440	2340 ± 960	59.9 ± 25.5	43800 ± 40400
	Group 4 (0.5% Gatifloxacin Ophthalmic Solution Treatment)			
	Conjunctiva (ng/g)	Cornea (ng/g)	Aqueous Humor (ng/mL)	Tears (ng/g)
0.25	4450 ± 3220	6770 ± 1220	161 ± 46	65400 ± 48200
0.5	5620 ± 5800	5780 ± 1870	214 ± 51	59700 ± 31100
1	1630 ± 1950	3640 ± 1010	272 ± 14	29100 ± 18400
2	1270 ± 1140	3890 ± 380	266 ± 35	15600 ± 7900
6	839 ± 819	405 0± 2750	97.5 ± 21.7	32100 ± 23400
12	1200 ± 500	1150 ± 200	39.7 ± 7.4	90500 ± 100000

*In summary:*

Pharmacokinetic studies in Dutch-Belted rabbits suggest that gatifloxacin exposure, expressed as AUC<sub>0-12hr</sub> (ng·h/g) in tears is comparable in ZYMAR® and 0.5% Gatifloxacin Ophthalmic Formulation, and is in excess of the MICs of most pathogens commonly associated with conjunctival bacterial infections (Table 1). Mean tear concentrations of gatifloxacin at 6 and 12 hours, following administration 0.5% Gatifloxacin Ophthalmic Formulation, also exceed the MICs for common ophthalmic pathogens. The Applicant has included no new data in this submission, from studies of gatifloxacin efficacy against ophthalmic pathogens in animal models.

**PHARMACOKINETIC / PHARMACODYNAMIC STUDIES**

In studies conducted to support NDA 21493, gatifloxacin ophthalmic solution 0.3% and 0.5% was topically administered to healthy subjects (increasing doses to 2 drops 8 times per day for 3 day), and was undetectable in serum samples. The Applicant has provided no new data in this submission, regarding the pharmacokinetic/pharmacodynamic behavior of gatifloxacin 0.5% ophthalmic solution in humans.

## CLINICAL TRIALS

The Applicant has submitted data from two Phase 3 clinical trials, designed to demonstrate the efficacy and safety of gatifloxacin ophthalmic solution 0.5%, compared to placebo, in the treatment of acute bacterial conjunctivitis in subjects  $\geq$  1 year of age, as measured by clinical success at Day 6 (5 days of dosing, followed by an exit visit). The trial designs (Table 5) were identical, and were titled, "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."

There were three scheduled Study Visits, including a Day 1 (Baseline) Visit, a Day 4 Visit, and a Day 6 Visit, that was to occur between 12 and 48 hours after the last dose of study drug. Study drug was self-administered, with subjects instructed to deliver 1 drop of study drug to each qualified eye every 2 hours up to 8 times on Day 1, and to deliver 1 drop of study drug to each qualified eye twice daily on Days 2 through 5. Unqualified eyes (eyes diagnosed with bacterial conjunctivitis after Day 1 but before Day 6) were treated with study drug in a similar manner (up to 8 drops on the day of diagnosis, and twice daily through Day 6).

Subjects included patients at least 1 year of age diagnosed with acute bacterial conjunctivitis in at least one eye, with a minimum of 2+ (moderate) conjunctival hyperemia and a minimum of 1+ (mild) discharge. Subjects with concomitant adenovirus infection (or adenovirus infection, only) were excluded. Viral testing was performed on conjunctival swabs, using an FDA-approved test for adenovirus antigen testing (RPS Adeno Detector™, (b) (4)). Subjects who had used antibiotics or corticosteroids during the 2 weeks prior to the baseline visit were also excluded.

Analysis study populations (excluding site 13020 in Study 005, except where noted), included:

The modified intent-to-treat (mITT) population consisted of the randomized patients who had a positive conjunctival culture in at least 1 eye at baseline. This was the primary population for efficacy analysis.

The per protocol (PP) population was a subset of the mITT population. It consisted of the randomized patients who had a positive conjunctival culture in at least 1 eye at baseline, with at least one follow up visit and no major protocol deviations.

The intent-to-treat (ITT) population consisted of the randomized patients.

[Source: This submission; Module 2.7.3.3, page 12]

The primary efficacy end point was clinical success at Day 6 (up to Day 6) in the pooled mITT population, with "clinical success" defined as complete clearing (a score of 0 on a 4-point scale) of both hyperemia and conjunctival discharge in the study eye from Day 1. Secondary efficacy variables included microbiological cure ("all bacterial species at Day 1 eradicated), and clinical improvement of ocular signs and symptoms.

A total of 1437 subjects were enrolled in the two phase 3 studies, with 681 randomized to the gatifloxacin arm (642 (94.3%) of these completed the study) and 684 randomized to the vehicle arm (639 (93.4%) completed the study). Demographics were statistically similar between the two study arms in both studies. Study 004 was predominantly Caucasian, while Study 005 was predominantly Asian. The mean age in Study 004 was lower (by approximately 10 years) than the mean age in Study 005, and the percentage of subjects in the 1-18 year age group was significantly lower in Study 004, compared to Study 005 (48.5% compared to 12.7%, for the two gatifloxacin arms).

**Table 5:** Phase 3 efficacy and safety studies of gatifloxacin ophthalmic solution 0.5% in the treatment of acute bacterial conjunctivitis

Study ID	Sites Enrolling Patients Location	Study Start Status (Date) Enrollment Total/Goal	Design Control Type	Study Medication	Regimen	Entry Criteria	Primary Efficacy Measure	Primary Efficacy End Point	Secondary Efficacy End Points
198782-004	51 sites US	20 Aug 2007 11 Jun 2008	Double masked Randomized Vehicle controlled Parallel group	Gatifloxacin ophthalmic solution 0.5% or vehicle	Day 1: 1 drop in each qualified eye every 2 hours up to 8 times Days 2-5: 1 drop BID	Severity of conjunctival hyperaemia $\geq 2$ and discharge $\geq 1$ in at least 1 eye <sup>a</sup> $\geq 1$ year of age	Clinical success: severity of conjunctival hyperaemia + discharge = 0	Clinical success at day 6 in mITT population (day 6 visit analysis)	Clinical success at day 6 in ITT and PP populations Clinical success at day 4 Microbiological cure Microbiological response Clinical improvement in ocular signs and symptoms
198782-005	29 sites India 10 sites US	07 Feb 2008 05 Jan 2009	Double masked Randomized Vehicle controlled Parallel group	Gatifloxacin ophthalmic solution 0.5% or vehicle	Day 1: 1 drop in each qualified eye every 2 hours up to 8 times Days 2-5: 1 drop BID	Severity of conjunctival hyperaemia $\geq 2$ and discharge $\geq 1$ in at least 1 eye <sup>a</sup> $\geq 1$ year of age	Clinical success: severity of conjunctival hyperaemia + discharge = 0	Clinical success at day 6 in primary mITT population <sup>b</sup> (up to day 6 analysis)	Clinical success at day 4 Microbiological cure Microbiological response Clinical improvement in ocular signs and symptoms

BID = twice daily; ITT = intent-to-treat population (randomized patients); mITT = modified ITT (all randomized patients with positive culture at baseline); PP = per protocol population (mITT patients with at least 1 follow up visit and no major protocol deviations)

a: Severity of conjunctival hyperaemia and mucopurulent discharge was measured on a 0-3 scale with 3 being the most severe

b: Excludes site 13020

Source: This application: Table 2.7.3.2-1

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**Table 6:** Qualified Eye(s) Used to Determine Efficacy by Analysis Method and Population

Efficacy Population	Analysis Method	
	Study Eye	Worse Eye
mITT/ PP <sup>a</sup>		
One eye culture positive at baseline	Culture positive eye	Culture positive eye
Both eyes culture positive at baseline	Right eye	Eye with greater baseline sum of scores for conjunctival hyperemia and discharge. If both eyes have the same sum, the right eye will be chosen.
ITT		
One eye qualified at baseline <sup>b</sup>	Qualified eye	Qualified eye
Both eyes qualified at baseline <sup>b</sup>	Right eye	Eye with highest baseline sum of scores for conjunctival hyperemia and discharge. If both eyes have the same sum, the right eye will be chosen.

a: Modified intent-to-treat population (mITT) included all randomized patients with at least 1 eye culture positive at baseline. The per protocol (PP) is a subset of mITT population.

b: Without regard to culture status.

Source: This Application; Module 2.7.3.3-1

Conjunctival specimens were collected by swab (swabs provided by the central laboratory) for bacteriologic testing (pathogen identification and antimicrobial susceptibility testing). Samples were collected from the qualified eye(s) at the baseline visit (prior to treatment), at Day 4, and at Day 6. All specimens were shipped to the central reference laboratory in transport media provided by the laboratory (tubed transport media consisting of phosphate buffered saline with 20% glycerol). Investigators were instructed on (b) (4) collection and shipping techniques, and were asked to ensure that all specimens be shipped, refrigerated or frozen, to the central

laboratory within 24 to 48 hours of collection. Specimens collected in the US (Study 004 and 10 sites in Study 005) were sent to (b) (4) for pathogen identification and quantification, as well as susceptibility testing by MIC and disk diffusion methods. Specimens collected in India were sent to (b) (4) for initial pathogen identification/quantification and susceptibility testing by disk diffusion methods (not reported), with isolates then shipped to (b) (4) for susceptibility testing by MIC and disk diffusion methods. Organism identification was performed using standard automated and manual methods. Laboratory manuals from both facilities (b) (4) were included for review, in this submission.

Susceptibility testing by MIC and Kirby-Bauer disk diffusion techniques was performed according to methods approved by CLSI (CLSI M100-S17 and CLSI M45-A) by (b) (4). All isolates were tested at the (b) (4) reference laboratory, with only those MIC results used in the data analysis for determination of microbiological efficacy. MIC testing was performed on in-house manufactured microtiter plates, with quality control performed on each day of testing. Comparator drugs included moxifloxacin, azithromycin, ciprofloxacin, erythromycin, gentamicin, tetracycline, and tobramycin.

Testing for adenovirus infection was performed by the investigator, locally, using the RPS Adeno Detector™ test kit. Specimens for adenovirus detection were collected at the Day 1 visit from qualified eye(s), after specimen collection was performed for bacteriologic testing. If an unqualified eye was diagnosed with bacterial conjunctivitis after the Day 1 visit, a specimen was collected for adenovirus detection (after collection of a specimen for bacteriologic testing).

Clinical significance of specific bacterial isolates was graded, based on threshold criteria developed by Liebowitz [Liebowitz 1991] (Table 7). Microbiological responses were defined based on bacteria identified at the baseline visit and present above threshold in cultures from that visit (Table 8). No molecular testing was performed to characterize "persistent" or "proliferating" bacteria, or to analyze the development of gatifloxacin resistance in such isolates.

**Table 7:** Pathological thresholds for common bacterial species

Group	Species Included	Pathological Threshold
Group I	<i>Acinetobacter</i> species, <i>Achromobacter</i> species, <i>Citrobacter</i> species, <i>Enterobacter</i> species, other Enterobacteriaceae, <i>Escherichia</i> species, <i>Haemophilus</i> species, (b) (4) species, <i>Moraxella</i> species (other than <i>Moraxella Branhamella catarrhalis</i> ), <i>Neisseria gonorrhoeae</i> , other <i>Neisseria</i> species, <i>Proteus/Morganella</i> species, <i>Pseudomonas aeruginosa</i> , other <i>Pseudomonas</i> species, <i>Serratia marcescens</i> , (b) (4) <i>Streptococcus pneumoniae</i>	(b) (4)
Group II	<i>Moraxella Branhamella catarrhalis</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus</i> Group B (beta or non-hemolytic), <i>Streptococcus</i> Group C (alpha, beta or non-hemolytic), <i>Streptococcus</i> Group D, <i>Streptococcus</i> Group G, <i>Streptococcus viridans</i>	(b) (4)
Group III	<i>Bacillus</i> species, <i>Micrococcus</i> species, <i>Staphylococcus epidermidis</i> , other coagulase-negative <i>Staphylococcus</i> species	(b) (4)
Group IV	<i>Corynebacterium</i>	(b) (4)

Source: This application; Module 5.3.5.1.4, Table 13.1.6

**Table 8: Classification of Microbial Response**

Classification	Definition
Eradication	The pathogen, originally present above threshold at Day 1 (Baseline), is absent in the follow-up culture
Reduction	The pathogen, originally present above threshold at Day 1 (Baseline), is reduced to a count below threshold in the follow-up culture
Persistence	The pathogen, originally present above threshold at Day 1 (Baseline), is reduced to a count below Day 1 (Baseline) count, but is above or equal to threshold in the follow-up culture
Proliferation	The pathogen, originally present above threshold at Day 1 (Baseline), is increased to a count above Day 1 (Baseline) count in the follow-up culture

Source: This application; Module 5.3.5.1.4, Table 13.1.7

## STUDY 004

Study 198782-004 ("Study 004") was conducted from 20 August 2007 through 11 June 2008. There were 578 enrolled subjects at 53 sites in the United States, with 287 randomized to receive gatifloxacin (167 of these subjects were culture positive), and 291 randomized to placebo (158 were culture positive). The number of subjects in each analysis population is summarized in Table 9. Demographic characteristics were similar in the gatifloxacin and vehicle arms. Most subjects were Caucasian (84% in both arms). The mean subject age was 30.7 for the gatifloxacin arm and 26.4 for the vehicle arm (mITT population).

**Table 9: Number of Patients in Each Analysis Population**

Population	Gatifloxacin	Vehicle
ITT <sup>a</sup>	287	291
Safety	288	289
mITT <sup>a</sup>	167	158
PP <sup>a</sup>	142	138

a: used for efficacy analyses

Source: This application; Module 5.3.5.1.3, Table 10-2

The ocular pathogens most frequently isolated from conjunctival cultures collected at baseline (mITT population) are summarized in Table 10. In Study 004, there were no collected isolates of (b) (4) or (b) (4) above threshold. (b) (4) (above threshold) was collected from one subject in the vehicle arm (none in the gatifloxacin arm).

**Table 10: Most Frequently Isolated Organisms Above Threshold at Baseline for Qualified Eye(s) (mITT population) (% of subjects with specific pathogen isolated at quantity over threshold)**

Organism	Gatifloxacin 0.5% (n = 167)	Vehicle (n = 158)	Total (n = 325)
<i>Haemophilus influenzae</i>	64 (38.3%)	48 (30.4%)	112
<i>Streptococcus pneumoniae</i>	43 (25.7%)	44 (27.8%)	87
<i>Staphylococcus aureus</i>	31 (18.6%)	24 (15.2%)	55
<i>Staphylococcus epidermidis</i>	23 (13.8%)	26 (16.5%)	49
<i>Streptococcus mitis</i> group	14 (8.4%)	8 (5.1%)	22
<i>Streptococcus oralis</i>	11 (6.6%)	5 (3.2%)	14
CDC coryneform group G	6 (3.6%)	6 (3.8%)	12
<i>Streptococcus mitis</i>	4 (2.4%)	6 (3.8%)	10

Source: Adapted from Table 14.5-9.1, this Application

Clinical success (scores of 0 for both conjunctival hyperemia and mucopurulent discharge) was achieved in 74.9% (125/167) of subjects in the gatifloxacin arm (mITT population), compared to 65.2% (103/158) in the vehicle arm (mITT population), with a P value of 0.057. An early effect (clinical success at Day 4) was noted in 33.5% of subjects in the gatifloxacin arm (mITT population), compared to 20.9% of the vehicle arm (mITT population).

The difference in microbiological cure was statistically significant, with cure demonstrated in 89.2% of subjects in the gatifloxacin arm, compared to 61.4% of subjects in the vehicle arm (Table 11).

**Table 11: Microbiological Cure in the Study Eye (mITT Population)**

Visit Time point	Day 6 Visit Analysis (Primary Analysis Method)			Up to Day 6 Analysis		
	Gatifloxacin (N = 167)	Vehicle (N = 158)	P Value <sup>a</sup>	Gatifloxacin (N = 167)	Vehicle (N = 158)	P Value <sup>a</sup>
Day 4 n/N (%)	145/167 (86.8)	81/158 (51.3)	< 0.001	145/167 (86.8)	81/158 (51.3)	<0.001
Day 6 n/N (%)	149/167 (89.2)	97/158 (61.4)	< 0.001	148/167 (88.6)	94/158 (59.5)	<0.001

Microbiological cure: all bacterial species present in the study eye at baseline were eradicated at the follow-up visit. "Up to Day 6 Analysis" excludes data collected after day 6.

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

Microbiological response, based on species identified at the baseline visit in the Study Eye, is summarized in Table 12. Eradication rates for all bacteria, Gram positive isolates, and Gram negative isolates were significantly higher in the gatifloxacin arm, compared to the vehicle arm. Microbiological response, listed by principle pathogens isolated in Study 004, is summarized in Table 13. Although no statistical analysis was performed, eradication rates for gatifloxacin against the principle ocular pathogens isolated in Study 004 were notably higher in the gatifloxacin arm, compared to vehicle (no P values reported), except against streptococcal species other than *S. pneumoniae* (eradication rates for both *S. mitis* group and *S. oralis* were 100% in both arms).

**Table 12: Microbiological Response in the Study Eye at Day 6 by Bacterial Class (mITT Population)**

Class/Microbiological Response	Day 6 Visit Analysis (Primary Analysis Method)		Up to Day 6 Analysis	
	Gatifloxacin (N= 167)	Vehicle (N= 158)	Gatifloxacin (N= 167)	Vehicle (N= 158)
All organisms				
n	209	189	145	131
Eradication	194 (92.8%)	136 (72.0%)	136 (93.8%)	99 (75.6%)
Reduction	3 (1.4%)	6 (3.2%)	3 (2.1%)	1 (0.8%)
Persistence	7 (3.3%)	39 (20.6%)	4 (2.8%)	26 (19.8%)
Proliferation	5 (2.4%)	8 (4.2%)	2 (1.4%)	5 (3.8%)
All gram-positive organisms				
n	135	135	96	92
Eradication	122 (90.4%)	103 (76.3%)	87 (90.6%)	75 (81.5%)
Reduction	3 (2.2%)	6 (4.4%)	3 (3.1%)	1 (1.1%)
Persistence	5 (3.7%)	21 (15.6%)	4 (4.2%)	13 (14.1%)
Proliferation	5 (3.7%)	5 (3.7%)	2 (2.1%)	3 (3.3%)
All gram-negative organisms				
n	74	54	49	39
Eradication	72 (97.3%)	33 (61.1%)	49 (100.0%)	24 (61.5%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	2 (2.7%)	18 (33.3%)	0 (0.0%)	13 (33.3%)
Proliferation	0 (0.0%)	3 (5.6%)	0 (0.0%)	2 (5.1%)

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See Section 9.5.1.2 for definitions of response categories.

“Up to Day 6 Analysis” excludes data collected after day 6.

n = number of species above pathological threshold at baseline with an evaluable response at the follow-up visit.

Source: This application; Module 5.3.5.1.3, Table 11-4

**Table 13:** Microbiological Response in the Study Eye by Most Frequent Organisms at the Day 6 Time Point (mITT Population)

Organism/Microbiological Response	Day 6 Visit Analysis (Primary Analysis Method)		Up to Day 6 Visit Analysis	
	Gatifloxacin (N= 167)	Vehicle (N= 158)	Gatifloxacin (N= 167)	Vehicle (N= 158)
<i>Haemophilus influenzae</i>				
n	62	46	40	31
Eradication	60 (96.8%)	26 (56.5%)	40 (100.0%)	17 (54.8%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	2 (3.2%)	17 (37.0%)	0 (0.0%)	12 (38.7%)
Proliferation	0 (0.0%)	3 (6.5%)	0 (0.0%)	2 (6.5%)
<i>Streptococcus pneumoniae</i>				
n	40	40	24	28
Eradication	35 (87.5%)	25 (62.5%)	21 (87.5%)	20 (71.4%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	3 (7.5%)	11 (27.5%)	2 (8.3%)	6 (21.4%)
Proliferation	2 (5.0%)	4 (10.0%)	1 (4.2%)	2 (7.1%)
<i>Staphylococcus aureus</i>				
n	23	18	16	9
Eradication	20 (87.0%)	13 (72.2%)	14 (87.5%)	7 (77.8%)
Reduction	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)
Persistence	2 (8.7%)	4 (22.2%)	2 (12.5%)	2 (22.2%)
Proliferation	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<i>Staphylococcus epidermidis</i>				
n	20	25	15	18
Eradication	16 (80.0%)	17 (68.0%)	12(80.0%)	13 (72.2%)
Reduction	3 (15.0%)	4 (16.0%)	3 (20.0%)	1 (5.6%)
Persistence	0 (0.0%)	3 (12.0%)	0 (0.0%)	3 (16.7%)
Proliferation	1 (5.0%)	1 (4.0%)	0 (0.0%)	1 (5.6%)
<i>Streptococcus mitis</i> group				
n	10	6	8	3
Eradication	10 (100.0%)	6 (100.0%)	8 (100.0%)	3 (100.0%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Proliferation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<i>Streptococcus oralis</i>				
n	7	4	5	3
Eradication	7 (100.0%)	4 (100.0%)	5 (100.0%)	3 (100.0%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Proliferation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table includes only the organisms most frequently identified at baseline.

A microbiological response was considered "eradicated" if the pathogen, originally present above threshold at baseline, was absent in the follow-up culture. "Up to Day 6 Analysis" excludes data collected after day 6.

n = number of patients with the given species above pathological threshold at baseline with an evaluable response at the follow-up visit.

Source: This application; Module 5.3.5.1.3, Table 11-5

Susceptibility results (MIC<sub>90</sub>) for primary ocular pathogens recovered from Study Eyes in Study 004 are summarized in Table 14. No analysis of the development of gatifloxacin resistance in isolates collected in Study 004 was presented in this Application. Review of data presented in the Individual Efficacy Response Data Listing (Module 5.3.5.1.21), suggests that the high MIC<sub>90</sub> values for staphylococcal isolates at Day 6, compared to Day 1, was due to failure of treatment to eradicate bacteria with comparatively high initial MIC values, rather than increasing resistance in specific isolates (Table 15), but since genotypic comparison of isolates was not performed, this conclusion is hypothetical. Also, in a significant number of cases, staphylococcal isolates (some with relatively high MIC values) were collected at the Day 6 visit, but not at previous visits (Day 1 and/or Day 4). This was common for other bacterial species, as well.

**Table 14:** Summary of susceptibility results (MIC<sub>90</sub>, mcg/ml) for frequently isolated bacteria in Study 004 (Study Eye isolates, mITT population)

Organism	Gatifloxacin 0.5%			Vehicle		
	Day 1	Day 4	Day 6	Day 1	Day 4	Day 6
<i>Haemophilus influenzae</i>	0.03 (n=63)	0.03 (n=3)	0.015 (n=2)	0.03 (n=47)	0.03 (n=25)	0.03 (n=22)
<i>Streptococcus pneumoniae</i>	0.25 (n=41)	0.25 (n=3)	0.25 (n=5)	0.25 (n=44)	0.25 (n=21)	0.25 (n=16)
<i>Staphylococcus aureus</i>	4.0 (n=28)	>8 (n=5)	>8 (n=5)	0.12 (n=21)	2 (n=14)	2 (n=6)
<i>Staphylococcus epidermidis</i>	2.0 (n=20)	4.0 (n=1)	>8 (n=2)	>8 (n=26)	2 (n=10)	2 (n=10)
<i>Streptococcus mitis</i> group	4.5 (n=10)	1.0 (n=4)	0.25 (n=2)	0.5 (n=7)	0.5 (n=5)	0.12 (n=1)
<i>Streptococcus oralis</i>	1 (n=8)	0.5 (n=2)	n/a (n=0)	0.5 (n=5)	1.0 (n=1)	0.5 (n=1)
CDC coryneform group G	0.25 (n=4)	n/a (n=0)	n/a (n=0)	0.25 (n=5)	n/a (n=0)	0.03 (n=2)
<i>Streptococcus mitis</i>	0.5 (n=4)	n/a (n=0)	0.5 (n=2)	0.5 (n=6)	0.25 (n=1)	0.5 (n=3)
All Gram negative	0.06 (n=75)	0.5 (n=7)	2 (n=4)	0.06 (n=54)	0.06 (n=33)	0.06 (n=26)
All Gram positive	0.5 (n=143)	4.0 (n=21)	6.5 (n=20)	0.5 (n=147)	2.0 (n=62)	0.5 (n=44)
All bacteria	0.5 (n=218)	4.0 (n=28)	4.0 (n=24)	0.5 (n=201)	0.5 (n=95)	0.5 (n=70)

Source: Adapted from Table 14.5-3.1, 14.5-4.1, this Application

**Table 15:** Gatifloxacin MIC results for Staphylococcal Isolates from Selected Subjects (Study Eye) from Study 004 (mITT population)

Site-Subject	Pathogen	Day 1 MIC (mcg/ml)	Day 4 MIC (mcg/ml)	Day 6 MIC (mcg/ml)
10011-1511	<i>S. aureus</i>	> 8	> 8	> 8
10030-1546	<i>S. aureus</i>	4	4	4
10032-1054	<i>S. epidermidis</i>	0.12	n/a (culture neg)	> 8

Source: Adapted from Individual Efficacy Response Data Listing, Table 16.2.6.8, this Application

Clinical success and microbiological cure, by organism, is summarized in Table 16 for the principle pathogens collected in Study 004. In some cases, the number of recovered pathogens of a particular species was too low to provide any useful information, e.g. 1 of 2 subjects in the gatifloxacin arm, with *Streptococcus oralis* identified at baseline (50%), resulted in microbiological cure, while 3 of 3 in the vehicle arm resulted in microbiological cure (100%). Against the

pathogens most associated with conjunctivitis (*S. aureus*, *S. epidermidis*, *S. pneumoniae*, and *H. influenzae*), rates of microbiological success generally correlated with rates of clinical success, in the two study arms.

**Table 16:** 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 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
<i>Haemophilus influenzae</i>	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)
<i>Staphylococcus aureus</i>	11/20 (55.0)	15/20 (75.0)	9/13 (69.2)	8/13 (61.5)	10/20 (50.0)	15/20 (75.0)	5/13 (38.5)	6/13 (46.2)
<i>Staphylococcus epidermidis</i>	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)
<i>Streptococcus pneumoniae</i>	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)
<i>Streptococcus mitis</i> 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)
<i>Streptococcus oralis</i>	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 <sup>a</sup>	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

<sup>a</sup> Patients with mixed infection are not included in rows for individual organisms.

Source: This Application; Module 5.3.5.1, Table 11-10

With regard to the principle pathogens included in the proposed label for ZYMAXID™, there were ≥10 isolates (with at least a 50% eradication) of *S. aureus*, *S. epidermidis*, *S. mitis* group, *S. pneumoniae*, and *H. influenzae* (see Table 13). There were between 5 and 9 isolates (with at least an 80% eradication rate) of *S. oralis*.

## STUDY 005

Study 198782-005 was conducted from 7 February 2008 (first subject enrolled) through 5 January 2009 (last subject completed). The study was conducted in the U.S. and India, with subjects enrolled at 10 sites in the U.S. (89 subjects) and 29 sites in India (770 subjects). At one site in India, cGCP violations were observed, generating concerns about data integrity. Prior to database lock, the Applicant decided to analyze efficacy data including and excluding data from site 13020 (72 subjects, 36 in each arm). Unless noted, efficacy data discussed in this review excludes data from site 13020.

The number of subjects in each analysis population is summarized in Table 17. Demographic characteristics were similar in the gatifloxacin and vehicle arms. Most subjects were non-Caucasian (96.0% in the gatifloxacin arm and 97.0% in the vehicle arm). The mean subject age was 38.9 for the gatifloxacin arm and 38.8 for the vehicle arm (mITT population).

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**Table 17: Number of Patients in Each Analysis Population**

Population	All Sites		Site 13020 Excluded	
	Gatifloxacin	Vehicle	Gatifloxacin	Vehicle
ITT	430	429	394	393
Safety	429 <sup>a</sup>	427 <sup>a</sup>	Not applicable	Not applicable
mITT	179	185	166 <sup>b</sup>	167 <sup>b</sup>
PP	173	174	160	156

a All sites were included in safety analyses.

b The mITT population excluding site 13020 was considered primary for efficacy analyses.

Source: This application; Module 5.3.5.1.3, Table 10-2

The ocular pathogens most frequently isolated from conjunctival cultures collected at baseline (mITT population) are summarized in Table 18.

**Table 18: Most Frequently Isolated Organisms Above Threshold at Baseline for Qualified Eye(s) (mITT population) (% of subjects with specific pathogen isolated at quantity over threshold)**

Organism	Gatifloxacin 0.5% (n = 166)	Vehicle (n = 167)	Total (n = 333)
<i>Staphylococcus aureus</i>	33 (20.5%)	24 (16.2%)	57
<i>Staphylococcus epidermidis</i>	30 (19.3%)	24 (15.0%)	54
<i>Staphylococcus hominis</i>	10 (6.0%)	16 (10.2%)	26

(b) (4)

<i>Pseudomonas aeruginosa</i>	7 (4.8%)	15 (9.6%)	22
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Source: Adapted from Table 14.5-9.1, this Application

Clinical success (scores of 0 for both conjunctival hyperemia and mucopurulent discharge) was achieved in 51.8% (86/166) of subjects in the gatifloxacin arm (mITT population), compared to 41.3% (69/147) in the vehicle arm (mITT population), with a P value of 0.055. An early effect (clinical success at Day 4) was noted in 13.9% (23/166) of subjects in the gatifloxacin arm (mITT population), compared to 10.2% (17/167) of the vehicle arm (mITT population), with a P value of 0.302.

The difference in microbiological cure was statistically significant, with cure demonstrated in 92.2% of subjects in the gatifloxacin arm, compared to 80.2% of subjects in the vehicle arm, with a P value of 0.002 (Table 19).

**Table 19: Microbiological Cure in the Study Eye (mITT Population)**

Population	Day 6 Visit Analysis			Up to Day 6 Analysis (Primary Analysis Method)		
	Gatifloxacin	Vehicle	P-value <sup>a</sup>	Gatifloxacin	Vehicle	P value <sup>a</sup>
mITT (LOCF)						
Day 4 n/N (%)	146/166 (88.0%)	123/167 (73.7%)	<0.001	144/166 (88.0%)	123/167 (73.3%)	<0.001
Day 6 n/N (%)	155/166 (93.4%)	136/167 (81.4%)	0.001	153/166 (92.2%)	134/167 (80.2%)	0.002
PP						
Day 4 n/N (%)	141/155 (91.0%)	117/147 (79.6%)	0.005	141/155 (91.0%)	117/147 (79.6%)	0.005
Day 6 n/N (%)	148/156 (94.9%)	122/143 (85.3%)	0.005	130/138 (94.2%)	111/131 (84.7%)	0.011

LOCF = last observation carried forward; mITT = modified intent-to-treat; PP = per protocol

Microbiological cure: all bacterial species present in the study eye at baseline were eradicated at the follow-up visit.

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

Source: This application; Module 5.3.5.1.3, Table 11-4

Microbiological response, based on species identified at the baseline visit in the Study Eye, is summarized in Table 20. Eradication rates for all bacteria, Gram positive isolates, and Gram negative isolates were marginally higher in the gatifloxacin arm, compared to the vehicle arm. Microbiological response, listed by principle pathogens isolated in Study 005, is summarized in Table 21. Eradication rates in the gatifloxacin arm were notably higher, compared to the vehicle arm, against *S. aureus*, but were only marginally higher or less than the rates for vehicle against other principle pathogens isolated in Study 005.

**Table 20:** Microbiological Response in the Study Eye at Day 6 by Bacterial Class (mITT Population)

Class/Microbiological Response	Day 6 Visit Analysis		Up to Day 6 Analysis (Primary Analysis Method)	
	Gatifloxacin	Vehicle	Gatifloxacin	Vehicle
All organisms				
n	176	179	150	154
Eradication	168 (95.5%)	154 (86.0%)	142 (94.7%)	133 (86.4%)
Reduction	3 (1.7%)	3 (1.7%)	3 (2.0%)	3 (1.9%)
Persistence	2 (1.1%)	13 (7.3%)	2 (1.3%)	12 (7.8%)
Proliferation	3 (1.7%)	9 (5.0%)	3 (2.0%)	6 (3.9%)
All gram-positive organisms				
n	145	131	122	114
Eradication	137 (94.5%)	108 (82.4%)	114 (93.4%)	94 (82.5%)
Reduction	3 (2.1%)	3 (2.3%)	3 (2.5%)	3 (2.6%)
Persistence	2 (1.4%)	12 (9.2%)	2 (1.6%)	12 (10.5%)
Proliferation	3 (2.1%)	8 (6.1%)	3 (2.5%)	5 (4.4%)
All gram-negative organisms				
n	31	48	28	40
Eradication	31 (100.0%)	46 (95.8%)	28 (100%)	39 (97.5%)
Reduction	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Persistence	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)
Proliferation	0 (0%)	1 (2.1%)	0 (0%)	1 (2.5%)

n = number of species above pathological threshold at baseline with an evaluable response at the follow-up visit.

Source: This application; Module 5.3.5.1.3, Table 11-5

**Table 21: Microbiological Response in the Study Eye by Most Frequent Organisms at the Day 6 Time Point (mITT Population)**

Organism/Microbiological Response	Day 6 Visit Analysis		Up to Day 6 Analysis (Primary Analysis Method)	
	Gatifloxacin	Vehicle	Gatifloxacin	Vehicle
<i>Staphylococcus aureus</i>				
n	33	24	32	20
Eradication	31 (93.9%)	17 (70.8%)	30 (93.8%)	15 (75.0%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	1 (3.0%)	2 (8.3%)	1 (3.1%)	2 (10.0%)
Proliferation	1 (3.0%)	5 (20.8%)	1 (3.1%)	3 (15.0%)
<i>Staphylococcus epidermidis</i>				
n	30	24	26	23
Eradication	28 (93.3%)	22 (91.7%)	24 (92.3%)	21 (91.3%)
Reduction	2 (6.7%)	0 (0.0%)	2 (7.7%)	0 (0.0%)
Persistence	0 (0.0%)	2 (8.3%)	0 (0.0%)	2 (8.7%)
Proliferation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gram positive cocci in clusters, isolated				
n	10	18	7	15
Eradication	7 (70.0%)	12 (66.7%)	4 (57.1%)	10 (66.7%)
Reduction	1 (10.0%)	3 (16.7%)	1 (14.3%)	3 (20.0%)
Persistence	0 (0.0%)	2 (11.1%)	0 (0.0%)	2 (13.3%)
Proliferation	2 (20.0%)	1 (5.6%)	2 (28.6%)	0 (0.0%)
<i>Pseudomonas aeruginosa</i>				
n	7	15	6	14
Eradication	7 (100.0%)	15 (100.0%)	6 (100.0%)	14 (100.0%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Proliferation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<i>Staphylococcus hominis</i>				
n	10	16	7	14
Eradication	9 (90.0%)	16 (100.0%)	6 (85.7%)	14 (100.0%)
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistence	1 (10.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)
Proliferation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Note: Table includes only the organisms most frequently identified at baseline.  
 n = number of species above pathological threshold at baseline with an evaluable response at the follow-up visit.  
 Source: This application; Module 5.3.5.1.3, Table 11-6

Susceptibility results for primary ocular pathogens recovered from Study Eyes in Study 005 are summarized in Table 22. No analysis of the development of gatifloxacin resistance in isolates collected in Study 005 was presented in this Application.

**Table 22:** Summary of susceptibility results (MIC<sub>90</sub>, mcg/ml) for frequently isolated bacteria in Study 005 (Study Eye isolates, mITT population)

Organism	Gatifloxacin 0.5%			Vehicle		
	Day 1	Day 4	Day 6	Day 1	Day 4	Day 6
<i>Staphylococcus aureus</i>	4.0 (n=33)	4.0 (n=5)	4.0 (n=2)	4.0 (n=27)	2.0 (n=13)	4.0 (n=7)
<i>Staphylococcus epidermidis</i>	2.0 (n=31)	0.12 (n=3)	4 (n=2)	2.0 (n=24)	4.0 (n=5)	4.0 (n=5)
<i>Staphylococcus hominis</i>	1.5 (n=10)	0.12 (n=1)	2.0 (n=4)	0.12 (n=16)	2.0 (n=3)	0.12 (n=3)
(b) (4)						
<i>Pseudomonas aeruginosa</i>	2.0 (n=8)	2.0 (n=1)	2.0 (n=1)	>8 (n=16)	>8 (n=3)	2.0 (n=2)
All Gram negative	>8 (n=32)	>8 (n=3)	2 (n=2)	>8 (n=51)	>8 (n=13)	2.0 (n=8)
All Gram positive	4.0 (n=132)	4.0 (n=15)	4.0 (n=12)	4.0 (n=118)	4.0 (n=35)	4.0 (n=33)
All bacteria	4.0 (n=164)	4.0 (n=18)	4.0 (n=14)	4.0 (n=169)	>8 (n=48)	4.0 (n=41)

Source: Adapted from Table 14.5-15.1, this Application

Clinical success and microbiological cure, by organism, is summarized in Table 23 for the principle pathogens collected in Study 005. Numbers of specific pathogens isolated in this study were relatively small and correlation between microbiological cure and clinical success is problematic. In the case of certain pathogens, included in the proposed label for ZYMAXID™ (*S. epidermidis*, [redacted], and *S. hominis*), microbiological cure rates (Day 6, mITT population) for subjects in the gatifloxacin arm were either less than or virtually identical to eradication rates for subjects in the vehicle arm.

**Table 23:** Clinical Success and Microbiological Cure in Study Eye by Organism at the Day 6 Time Point (Up to Day 6 Analysis of the mITT Population)

Organism	Gatifloxacin		Vehicle	
	Clinical Success n/N (%)	Microbiological Cure n/N (%)	Clinical Success n/N (%)	Microbiological Cure n/N (%)
<i>Staphylococcus aureus</i>	16/32 (50.0%)	30/32 (93.8%)	8/24 (33.3%)	16/24 (66.7%)
<i>Staphylococcus epidermidis</i>	15/28 (53.6%)	26/28 (92.9%)	8/18 (44.4%)	17/18 (94.4%)
Gram positive cocci in clusters <sup>a</sup>	6/12 (50.0%)	7/12 (58.3%)	10/22 (45.5%)	12/22 (54.5%)
<i>Staphylococcus hominis</i>	3/7 (42.9%)	7/7 (100%)	7/15 (46.7%)	15/15 (100%)
<i>Pseudomonas aeruginosa</i>	2/6 (33.3%)	5/6 (83.3%)	3/9 (33.3%)	9/9 (100%)
Mixed infection total <sup>b</sup>	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 or gram positive cocci in clusters.

Source: This application; Module 5.3.5.1, Table 11-11

With regard to the principle pathogens included in the proposed label for ZYMAXID™, there were ≥10 isolates (with at least a 50% eradication) of *S. aureus*, *S. epidermidis*, (b) (4), and (b) (4) (see Table 21). There were between 5 and 9 isolates (with at least an 80% eradication rate) of *S. hominis*. Of these pathogens, no isolates of (b) (4) or (b) (4) were seen in subjects treated in the U.S. (in either pivotal trial).

**SUMMARY OF CLINICAL STUDIES**

Studies 004 and 005 were performed according to identical protocols, with Study 004 conducted solely in the U.S. (578 subjects enrolled) and Study 005 conducted primarily in India (770 subjects enrolled at 29 sites in India, 89 subjects enrolled at 10 sites in the U.S.). Both studies consisted of 3 scheduled office visits (Day 1, Day 4, and Day 6), both studies compared treatment with gatifloxacin 0.5% to gatifloxacin vehicle (1:1 allocation), and both studies included identical dosing regimens (up to 8 drops (1 every 2 hours) on Day 1, followed by 1 drop BID on Days 2 through 5). The primary efficacy end point in both studies was clinical success at Day 6. Microbiological response (eradication of pathogens recovered at Day 1, in quantities exceeding threshold criteria) was a secondary efficacy endpoint.

Significant differences in studies included the age of subjects seen, with subjects enrolled in Study 005 approximately 10 years older than subjects enrolled in Study 004, and demographics (with the majority of subjects in Study 005 being Asian, while the majority of subjects in Study 004 were Caucasian). Significant differences also included the variety of principle pathogens seen in the two studies. Specific pathogens commonly associated with bacterial conjunctivitis, including *H. influenzae* and *S. pneumoniae*, were not isolated from in subjects seen by investigators at Indian sites, while pathogens uncommonly associated with bacterial conjunctivitis diagnosed in the U.S. (including coliform Gram negative rods, *P. aeruginosa*, and *Acinetobacter* species) were isolated from subjects seen at Indian sites, but rarely or never from subjects seen at U.S. sites. Gatifloxacin susceptibility results for principle pathogens listed in summary tables were generally higher against isolated recovered from specimens collected in Subject 005, compared to isolates

from Study 004. There was higher baseline severity of mucopurulent discharge noted in subjects in Study 005, compared to Study 004.

Clinical success in the two trials (pooled data) is summarized in Table 24. Using the up to Day 6 analysis method (mITT population), clinical success in the gatifloxacin treatment group was 58.0% and clinical success in the vehicle treatment group was 45.5% (p = 0.001). Clinical success for the individual trials is summarized in Table 25. Statistical significance between the two treatment groups (mITT population) was demonstrated in Study 004, but not Study 005.

**Table 24:** Clinical success in the study eye (up to Day 6 analysis of pooled data)

Population/ Time point	Gatifloxacin n/N (%)	Vehicle n/N (%)	P Value <sup>a</sup>
mITT (LOCF)			
Day 4	79/333 (23.7)	50/325 (15.4)	0.007
<b>Day 6</b>	<b>193/333 (58.0)</b>	<b>148/325 (45.5)</b>	<b>0.001</b>
PP			
Day 4	71/292 (24.3)	48/283 (17.0)	0.030
Day 6	156/240 (65.0)	128/228 (56.1)	0.050
ITT (LOCF)			
Day 4	171/681 (25.1)	145/684 (21.2)	0.087
Day 6	390/681 (57.3)	341/684 (49.9)	0.006

Bolding shows the primary comparison.

Clinical success: sum of severity of conjunctival hyperaemia and conjunctival discharge = 0

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

Source: This application: Table 2.7.3.3-4

**Table 25:** Clinical success in the study eye (up to Day 6 analysis of Phase 3 studies)

Population/ Time point	Study 004			Study 005		
	Gatifloxacin n/N (%)	Vehicle n/N (%)	P Value <sup>a</sup>	Gatifloxacin n/N (%)	Vehicle n/N (%)	P Value <sup>a</sup>
mITT (LOCF)						
Day 4	56/167 (33.5)	33/158 (20.9)	0.011	23/166 (13.9)	17/167 (10.2)	0.302
Day 6	107/167 (64.1)	79/158 (50.0)	0.010	86/166 (51.8)	69/167 (41.3)	0.055
PP						
Day 4	48/137 (35.0)	32/135 (23.7)	0.040	23/155 (14.8)	16/148 (10.8)	0.295
Day 6	80/102 (78.4)	67/94 (71.3)	0.248	76/138 (55.1)	61/134 (45.5)	0.115
ITT (LOCF)						
Day 4	106/287 (36.9)	87/291 (29.9)	0.073	65/394 (16.5)	58/393 (14.8)	0.502
Day 6	190/287 (66.2)	157/291 (54.0)	0.003	200/394 (50.8)	184/393 (46.8)	0.269

Clinical success: sum of severity of conjunctival hyperaemia and conjunctival discharge = 0

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

Source: This application: Table 2.7.3.3-5

The most common pathogens isolated at baseline (at quantities above threshold) are summarized, along with their gatifloxacin susceptibility results (MIC<sub>90</sub>), in Table 26. As described above, significant disparities were noted between the bacterial species identified in the two trials, as well as in the overall activity of gatifloxacin against the analyzed isolates. Of note, there were 16 isolates of *H. influenzae* and 7 isolates of *S. pneumoniae*, listed in the Study 005 column (all collected from subjects seen in the U.S.), compared to 169 and 127 of these species, respectively, that were seen in Study 004. Similarly, only 1 coliform bacteria (b) (4)

was listed for Study 004 (and only present in the vehicle arm), while 33 (b) (4) and *E. cloacae* were listed for Study 005 (all collected at Indian sites). *Acinetobacter* species (n = 0 for Study 004, n = 5 for Study 005) and *P. aeruginosa* (n = 2 for Study 004, n = 27 for Study 005) were also more predominant in Study 005. The number of gatifloxacin non-susceptible isolates (as indicated by calculated MIC<sub>90</sub> values) was also significantly greater in Study 005. Of note, the MIC<sub>90</sub> for (b) (4) (included in the proposed label) was ≥8 mcg/ml, for isolates collected in Study 005. Similarly, the MIC<sub>90</sub> values for isolates of *S. aureus* and (b) (4) (also included in the proposed label), collected in Study 005, were 4 mcg/ml and 8 mcg/ml, respectively. All of these values are considered resistant to gatifloxacin, according to CLSI M100-S20 [CLSI 2010].

**Table 26:** Baseline susceptibility (mcg/ml) to gatifloxacin for organisms in any qualified eye (mITT population)

Organism	Study 004		Study 005		Pooled	
	n	MIC <sub>90</sub> <sup>a</sup>	n	MIC <sub>90</sub> <sup>a</sup>	n	MIC <sub>90</sub> <sup>a</sup>
<i>Acinetobacter baumannii</i>	0	NA	5	8.0000	5	8.0000
CDC Coryneform Group G	14	0.2500	0	NA	14	0.2500
<i>Corynebacterium macginleyi</i>	3	0.060	3	0.5000	6	0.5000
<i>Corynebacterium propinquum</i>	6	8.0000	3	0.5000	9	8.0000
<i>Corynebacterium pseudodiphtheriticum</i>	9	0.5000	0	NA	9	0.5000
<i>Corynebacterium striatum</i>	3	4.0000	3	4.0000	6	4.0000
<i>Enterobacter cloacae</i>	0	NA	5	2.0000	5	2.0000
<i>Enterococcus faecalis</i>	4	0.5000	1	1.0000	5	1.0000
<i>Haemophilus influenzae</i>	169	0.0300	16	0.0300	185	0.0300
(b) (4)						
<i>Moraxella lacunata</i>	5	0.0600	0	NA	5	0.0600
<i>Pseudomonas aeruginosa</i>	2	1.0000	27	>8	29	>8
<i>Staphylococcus arlettae</i>	0	NA	8	0.5000	8	0.5000
<i>Staphylococcus aureus</i>	63	0.2500	67	4.0000	130	4.0000
<i>Staphylococcus epidermidis</i>	56	2.0000	63	2.0000	119	2.0000
(b) (4)						
<i>Staphylococcus hominis</i>	2	0.1200	29	1.0000	31	0.2500
<i>Staphylococcus warneri</i>	5	0.2500	13	8.0000	18	8.0000
(b) (4)						
<i>Streptococcus mitis</i>	12	0.5000	2	0.5000	14	0.5000
<i>Streptococcus mitis</i> group	23	0.5000	4	0.5000	27	0.5000
<i>Streptococcus oralis</i>	17	0.5000	8	1.000	25	1.0000
<i>Streptococcus parasanguinis</i>	3	0.5000	2	0.5000	5	0.5000
<i>Streptococcus pneumoniae</i>	127	0.2500	7	0.2500	134	0.2500
<i>Streptococcus pyogenes</i>	1	0.2500	4	0.2500	5	0.2500
<i>Streptococcus salivarius</i>	5	0.5000	3	0.5000	8	0.5000
Viridans streptococci	10	0.3750	0	NA	10	0.3750

Includes organisms identified above threshold in ≥5 patients at baseline in the pooled mITT population. Treatment groups were combined. Sensitivity testing was conducted for organisms above pathological threshold only.

a: MIC<sub>90</sub> to gatifloxacin in µg/mL

Source: Module 5.3.5.3 ISE Table 1-58.3 and 1-58.4

Source: This submission, Table 2.7.3.3-23

Clinical success and microbiological cure, for the pooled population (mITT), by bacterial species, is summarized in Table 27. As with the analysis of the separate trials (above) general conclusions concerning the association of bacterial eradication (microbiological cure) and clinical success are not statistically meaningful, but may indicate an association, with higher levels of clinical success and microbiological cure noted in the gatifloxacin arm, with regard to most principle ocular pathogens (e.g. *S. aureus*, *S. pneumoniae*, *H. influenzae* and *S. epidermidis*).

**Table 27:** Clinical success and microbiological cure in study eye by organism at the Day 6 time point (up to Day 6 analysis of the pooled mITT population, LOCF)

Organism	Gatifloxacin		Vehicle	
	Clinical Success n/N (%)	Microbiological Cure <sup>a</sup> n/N (%)	Clinical Success n/N (%)	Microbiological Cure <sup>a</sup> n/N (%)
Gram-positive bacilli isolated <sup>b</sup>	2/5 (40.0)	5/5 (100)	0/0 (0.0)	0/0 (0.0)
Gram-positive cocci in clusters <sup>b</sup>	6/12 (50.0)	7/12 (58.3)	10/22 (45.5)	12/22 (54.5)
<i>Haemophilus influenzae</i>	38/43 (88.4)	42/43 (97.7)	19/45 (42.2)	26/45 (57.8)
(b) (4)				
<i>Pseudomonas aeruginosa</i>	2/7 (28.6)	6/7 (85.7)	4/10 (40.0)	9/10 (90.0)
<i>Staphylococcus aureus</i>	26/52 (50.0)	45/52 (86.5)	13/37 (35.1)	22/37 (59.5)
<i>Staphylococcus epidermidis</i>	21/35 (60.0)	31/35 (88.6)	14/27 (51.9)	22/27 (81.5)
(b) (4)				
<i>Staphylococcus hominis</i>	3/7 (42.9)	7/7 (100)	7/15 (46.7)	15/15 (100)
<i>Staphylococcus warneri</i>	5/11 (45.5)	10/11 (90.9)	1/2 (50.0)	2/2 (100.0)
(b) (4)				
<i>Streptococcus oralis</i>	2/5 (40.0)	4/5 (80)	1/4 (25.0)	4/4 (100)
<i>Streptococcus pneumoniae</i>	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.

Source: This submission; Module 2.5, Table 2.5.4-6

Using pooled data from the two studies (Table 28) and individual analysis of the separate studies (Table 29), microbiological cure was demonstrated at both the Day 4 and Day 6 time points (Table 28).

**Table 28:** Microbiological Cure in the Study Eye in the mITT Population (Up to Day 6 Analysis of Pooled Data, LOCF)

Time point	Gatifloxacin n/N (%)	Vehicle n/N (%)	P Value <sup>a</sup>
Day 4	291/333 (87.4)	204/325 (62.8)	< 0.001
Day 6	301/333 (90.4)	228/325 (70.2)	< 0.001

Microbiological cure = all bacterial species present above threshold in the study eye at baseline were eradicated.

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.

Source: This submission, Table 2.7.3.3-15

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**Table 29:** Microbiological Cure in the Study Eye in the mITT Population (Up to Day 6 Analysis of Phase 3 Studies, LOCF)

Time point	Study 004			Study 005		
	Gatifloxacin n/N (%)	Vehicle n/N (%)	P Value <sup>a</sup>	Gatifloxacin n/N (%)	Vehicle n/N (%)	P Value <sup>a</sup>
Day 4	145/167 (86.8)	81/158 (51.3)	< 0.001	146/166 (88.0)	123/167 (73.7)	< 0.001
Day 6	148/167 (88.6)	94/158 (59.5)	< 0.001	153/166 (92.2)	134/167 (80.2)	0.002

Microbiological cure = all bacterial species present above threshold in the study eye at baseline were eradicated.

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

Data collected in Studies 004 and 005, analyzed separately and as pooled data, support the inclusion of *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus pneumoniae*, *S. mitis* group, *S. oralis*, and *H. influenzae* in the proposed label for ZYMAXID™. Each of these species has been associated with bacterial conjunctivitis in the current literature, and each was isolated in quantities above established threshold levels, as proposed at IND discussions prior to this Application. Each was associated with adequate microbiological cure based on the number of isolates seen, e.g. 5-9 isolates with  $\geq 80\%$  eradication or  $\geq 10$  isolates with  $\geq 50\%$  eradication. Although no information regarding the in vitro activity of gatifloxacin against recent isolates of ocular pathogens was submitted in this NDA (other than data from Phase 3 clinical trials), and the MIC<sub>90</sub> of gatifloxacin against certain pathogens (notably *S. aureus*) exceeded current CLSI susceptibility breakpoints, exposure to the antimicrobial is expected to far exceed breakpoint levels. Inclusion of (b) (4) (b) (4) in the proposed label for ZYMAXID™ is not supported by the data included in this Application. No isolates of these ocular pathogens were recovered from gatifloxacin-treated subjects seen in the U.S.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
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NDA No. 022548  
Gatifloxacin for bacterial conjunctivitis  
Date Review Completed: 24 February 2010

Page 36 of 36  
Clinical Microbiology Review

F. Marsik, Ph.D.  
Micro TL/HFD-520  
24 Feb 10 FIN FJM

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

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KERRY SNOW  
02/25/2010

FREDERIC J MARIK  
02/25/2010

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number: 22-548**

**Applicant: Allergan, Inc.**

**Submit Date: 30 July 2009**

**Drug Name: Gatifloxacin  
Ophthalmic Solution, 0.5%**

**NDA Type: 505(b)(1)**

**Received Date: 30 July 2009**

The following are necessary to initiate a review of the NDA application:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	<b>X</b>		Submission is in eCTD format. All applicable links are functioning
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	<b>X</b>		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	<b>X</b>		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		<b>X</b>	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	<b>X</b>		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	<b>X</b>		
7	Has the applicant submitted the results of analytical method verification studies?	<b>X</b>		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	
9	Is this NDA fileable? If not, then describe why.	<b>X</b>		

**Additional Comments:** The NDA was submitted in eCTD format and is available via the Global Submit file system.

From a microbiological product quality perspective, the applicant appears to have submitted the requisite documentation for review of manufacturing and controls for the above described drug product. This NDA submission is fileable from a Microbiology Product Quality standpoint.

**Comment to be submitted to the Applicant:** It is the expectation of the Division that ophthalmic drug products have a specification for bacterial endotoxins not to exceed (b) (4). The submitted specification for bacterial endotoxins in the drug product (b) (4) is too high and should

be reduced to (b) (4). Considering that the limit of detection for the assay provided in the application is (u) (4), a specification of 0.5 EU/ml should be assayable with the current methods.

01 SEPTEMBER 2009

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Robert J. Mello, Ph.D.  
Reviewing Microbiologist

Date

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Stephen E. Langille, Ph.D.  
Senior Microbiology Reviewer

Date

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ROBERT J MELLO  
09/18/2009

STEPHEN E LANGILLE  
09/21/2009

**Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability  
NDA 22-548: Gatifloxacin Ophthalmic Solution for Bacterial  
Conjunctivitis**

**Reviewer: Kerry Snow**

**Date Review completed: 28 August 2009**

On initial overview of the NDA application for RTF:

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		Preclinical and nonclinical (in vitro) microbiology data is not provided in this submission (only as reference to NDA 21493)
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		See #1
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		See #1
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		See #1; no in vitro data has been submitted to support inclusion of pathogens in the label "second list"
5	Has the applicant <u>submitted</u> draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓		n/a
6	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	✓		

**Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability  
NDA 22-548: Gatifloxacin Ophthalmic Solution for Bacterial  
Conjunctivitis**

**Reviewer: Kerry Snow**

**Date Review completed: 28 August 2009**

8	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in a format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	<b>FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? IF NO, GIVE REASONS BELOW.</b>	✓		

**Any Additional Clinical Microbiology Comments:** No clinical microbiology data is included in this submission, other than data from two Phase 3 clinical trials and two animal (rabbit) efficacy studies.

**Reviewing Clinical Microbiologist:** Kerry Snow

F. Marsik, Ph.D.  
TLMicro/HFD-520  
2 Sep 09 FIN FJM

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KERRY SNOW  
09/02/2009

FREDERIC J MARSIK  
09/03/2009