CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22428Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

19 JULY 2010

NDA: 22-428/N-000 (Supporting Document #13)

Drug Product Name

Proprietary: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution

Non-proprietary: moxifloxacin hydrochloride ophthalmic solution 0.5% as base

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
21 JUNE 2010	22 JUNE 2010	24 June 2010	30 June 2010

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
12 December 2008 10 February 2009	1	28 September 2009

Applicant/Sponsor

Name: Alcon Pharmaceuticals Ltd.

Address: Route des Arsenaux 41
1700 Fribourg
Switzerland

Representative: Karen S. Lankow
Assoc. Dir. Regulatory Affairs
Alcon Research Ltd.
6201 South Freeway
Fort Worth, TX 76134-2099

Telephone: 817-568-6494

Name of Reviewer: Robert J. Mello, Ph.D.

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

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA 505(b)(1)

2. SUBMISSION PROVIDES FOR: Marketing Authorization

3. MANUFACTURING SITE:
Drug Product Manufacturing and Testing Facility:
Alcon Research, Ltd.
ASPEX Manufacturing facility
6201 south Freeway
Fort Worth, TX 76134

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile solution; topical ocular; 0.5% as base (0.545% w/v). (b) (4) 3ml fill volumes in 4ml DROP-TAINER plastic containers.

5. METHOD(S) OF STERILIZATION: (b) (4) Processing subsequent to: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Antibacterial agent

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Review #1 for NDA 21-598/SCM-013 (for VIGAMOX), report dated 13 December 2006 (DARRTS date 14 December 2006).
- Microbiology Review #1 for NDA 21-598/SCM-016 (for VIGAMOX), report dated 02 MAY 2008 (DARRTS date 05 MAY 2008).
- Microbiology Review #1 for (b) (4) (Moxifloxacin HCl Ophthalmic Solution, 0.5%) report dated 12 March 2003 (DARRTS date 21 MARCH 2003).

C. REMARKS:

- The submission is a response to "COMMENTS" made by this reviewer during the original review.
- The submission is a paper technical submission (single white binder) not in CTD format.

Filename: N022428N000R2.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 (b) (4) (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.

B. Endorsement Block: _____
John W. Metcalfe, Ph.D.

C. CC Block
NDA 22-428

1 page has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22428	ORIG-1	ALCON PHARMACEUTICALS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

ROBERT J MELLO
07/19/2010

JOHN W METCALFE
07/19/2010
I concur.

Division of Anti-Infective and Ophthalmology Products
Clinical Microbiology Review

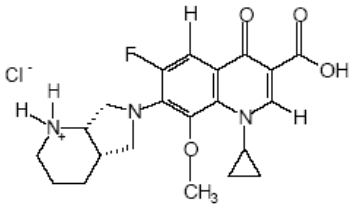
NDA: 022428
Date Company Submitted: 20 May 2010
Date Assigned: 24 May 2010
Date Completed: 14 July 2010
Reviewer: Kerry Snow MS

NAME AND ADDRESS OF APPLICANT:
Alcon Pharmaceuticals Ltd.
Route des Arsenaux 41
1700 Fribourg
Switzerland

CONTACT PERSON:
US Agent:
Alcon Research Ltd.
Mail Code R3-52
6201 South Freeway
Fort Worth, TX 76134-2099
Karen Lankow, Assoc. Director, Regulatory Affairs
817-568-6494

DRUG PRODUCT NAMES:
Proprietary Name: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution
Proposed Trade Name: Moxifloxacin AF
Code Names: AL-15469A (Alcon); BAY 12-8039 (Bayer)
Established Name: Moxifloxacin hydrochloride ophthalmic solution 0.5% as base (equivalent to 5 mg moxifloxacin per mL)
Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolol[3,4-*b*]pyridine-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

STRUCTURAL FORMULA:



MOLECULAR FORMULA:
$C_{21}H_{24}FN_3O_4 \cdot HCl$

MOLECULAR WEIGHT:
437.9

DRUG CATEGORY:
Antimicrobial

PROPOSED DOSAGE FORM AND STRENGTH:
Sterile ophthalmic solution of moxifloxacin hydrochloride, 0.5% as base
3 mL in a 4 mL bottle

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:
Instill 1 drop in the affected eye(s) 2 times daily for 7 days

DISPENSED:
Rx

PROPOSED INDICATION:
Treatment of bacterial conjunctivitis

RELATED DOCUMENTS:
NDA 021085 Avelox (original approval 10 December 1999)
NDA 021598 Vigamox (original approval 15 April 2003)
(b) (4) Vigamox
NDA 22428 Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution, 0.5% (original submission; review filed 24 August 2009)

TYPE OF SUBMISSION:
New Drug Application

PURPOSE OF SUBMISSION:

This New Drug Application (NDA) resubmission is submitted to seek approval for the use of an alternative formulation of moxifloxacin hydrochloride ophthalmic solution (Moxifloxacin AF) for the treatment of bacterial conjunctivitis in adults and pediatric patients one year or older. The original NDA was submitted on 12 December 2008. A Complete Response was issued by the Agency on 7 October 2009, identifying lack of substantial evidence of efficacy and recommending at least one additional clinical study. The current submission addresses the principle deficiency identified in the Complete Response, presenting data from an additional clinical study (C-07-40).

REMARKS:

The current submission includes only clinical data relevant to Study C-07-40. The clinical microbiology review of the original submission was filed on 24 August 2009.

This review is based on information submitted by the Applicant on May 20, 2010 (NDA 22428, resubmission), including the Applicant's summaries of studies performed to support the NDA, and microbiological data provided by the central testing laboratory, (b) (4) (b) (4) ((b) (4) (b) (4) This review does not address methods of moxifloxacin susceptibility testing or quality control parameters that would be employed during those procedures. Breakpoints for antimicrobial susceptibility testing are not required for antimicrobials intended for topical administration, and these have not been proposed in this NDA. Criteria for inclusion of organisms in the proposed label was discussed with the Applicant prior to the submission of this NDA ["organisms that are cultured from an eye with conjunctivitis and treated with Moxifloxacin AF in 5 or more cases with a ≥ 80% eradication rate or cultured from an eye with conjunctivitis and treated with Moxifloxacin AF in 10 or more cases with a ≥ 50% eradication rate"]. These criteria have been used in this review to determine the appropriate organisms for inclusion in the INDICATIONS AND USAGE section of the proposed label. The Applicant has provided summary information from recent literature to support inclusion of "second list" microorganisms in the proposed label.

The Applicant has referenced NDA 21-598 for VIGAMOX (Alcon Research, LTD) and NDA 21-085 for moxifloxacin hydrochloride tablets (Bayer Corporation) in support of the Application, and

has provided documentation for rights of reference. The Applicant has also referenced the original submission of NDA 22428 (submitted December 12, 2008; clinical microbiology review filed on August 24, 2009).

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).

(b) (4)

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. IN VITRO INFORMATION

MECHANISM OF ACTION

The Applicant has no additional information regarding the mechanism of action of moxifloxacin. Reference is made to the NDA 22428 original submission.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

In in vitro studies, using systemic interpretation criteria for antimicrobial activity, moxifloxacin has demonstrated activity against bacteria commonly associated with bacterial conjunctivitis, including *Staphylococcus aureus*, *S. epidermidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Propionibacterium acne*. These organisms, as well as others listed in the proposed label, should be susceptible to moxifloxacin at the concentration that is available per drop of solution (0.25 mg/drop). Data from in vitro susceptibility testing of isolates collected during Phase 3 clinical trials supports the inclusion of these and the other bacteria listed in the proposed indications for Moxifloxacin AF Ophthalmic Solution. In the original submission of this NDA, the Applicant provided a summary of data describing the in vitro activity of moxifloxacin against bacterial isolates not recovered in sufficient quantities from the two clinical trials. This data, collected from over 300 recent publications, supports the inclusion of these microorganisms in the proposed label's "second list" of bacteria, where in vitro data are available but their clinical significance in ophthalmic infections is unknown, and where the safety and effectiveness of Moxifloxacin AF has not been established. The concentration of moxifloxacin in Moxifloxacin AF Ophthalmic Solution is 5 mg/mL. At the recommended dose (0.50 mg moxifloxacin in 2 drops) initial exposure of the antibiotic is in significant excess, compared to the MIC_{range} of all pathogens listed in the proposed label. The current submission includes no additional data describing the in vitro activity of moxifloxacin against bacteria associated with conjunctival infection, except data collected in clinical study C-07-40.

RESISTANCE STUDIES

The Applicant has submitted no new information regarding the mechanisms of resistance to moxifloxacin among isolates commonly associated with bacterial conjunctivitis. Recent studies, including literature surveys compiled by the Applicant (presented in the original submission), suggest decreased susceptibility to moxifloxacin in certain bacterial species, including *Staphylococcus epidermidis* and some *Corynebacterium* species. No development of resistance to moxifloxacin was noted in the three clinical trials of Moxifloxacin AF Ophthalmic Solution.

II. HUMAN AND ANIMAL STUDIES

ANIMAL DISEASE MODELS

Moxifloxacin AF is effective at reducing bacterial counts (quinolone-susceptible and –resistant *S. aureus*, and *P. aeruginosa*), relative to untreated controls, in the corneas of New Zealand white rabbits, in both late- and early-stage therapy. Moxifloxacin AF is also effective, relative to untreated controls, when administered prior to infection (prophylactically) at 30 minutes pre-infection with quinolone-susceptible *S. aureus*, 8 hours pre-infection with quinolone-resistant *S. aureus,* and 3 hours pre-infection with *P. aeruginosa*. Moxifloxacin was statistically similar to the untreated control in a prophylaxis administered 3 hours prior to infection with quinolone-susceptible *S. aureus*.

The Applicant has provided no information in the current submission, regarding moxifloxacin efficacy in animal models of infection.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

Experiments in New Zealand white rabbits suggest that Moxifloxacin AF attains high concentrations in both tear film and aqueous humor following a single dose of the antimicrobial, and that levels in both fluids exceed those of VIGAMOX administered identically. Clinical trials in healthy human subjects suggest that Moxifloxacin AF administration over a dosing interval results in lower systemic exposure compared to that of VIGAMOX. Clinical trials in patients undergoing cataract surgery suggest that higher concentrations of moxifloxacin in conjunctival tissue are achieved more rapidly in patients receiving Moxifloxacin AF therapy, compared to those receiving VIGAMOX therapy, and that drug exposure, measured as AUC_{0-3}, is higher in Moxifloxacin AF-treated patients.

III. CLINICAL TRIALS

Data from three Phase 3 clinical trials submitted in support of the Application suggest that Moxifloxacin AF Ophthalmic Solution, 0.5% is effective in eradicating the principle pathogens associated with bacterial conjunctivitis. Eradication rates for all principle pathogens commonly associated with bacterial conjunctivitis were approximately 90% or higher. In cases where *Staphylococcus epidermidis* was isolated (an organism with potential non-susceptibility to fourth-generation fluoroquinolones), 92.9% of the pathogens were eradicated. Increased resistance to moxifloxacin was not noted in isolates defined as persistent pathogens in Study C-07-40 or Study C -04-38 (no persistent pathogens were identified in Study C-04-40).

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) 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_3 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 (Ocuflox), and besifloxacin (Besivance).

Moxifloxacin hydrochloride (Avelox) was approved in 1999 (NDA 21-085) as an oral tablet for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and mild to moderate community-acquired pneumonia, and was later approved for the treatment of uncomplicated skin and skin structure infections. Alcon referenced NDA 21-085 in its application for Vigamox (moxifloxacin hydrochloride solution/drops; ophthalmic, NDA 21-598), which was approved in 2003 for the treatment of bacterial conjunctivitis.

MOXIFLOXACIN ALTERNATIVE FORMULATION (AF) OPHTHALMIC SOLUTION

This application references NDA 21-085 (Avleox) and NDA 21-598 (VIGAMOX). The Applicant is submitting this NDA for an alternative formulation of moxifloxacin hydrochloride ophthalmic solution. Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution is intended to (b) (4) (b) (4) (b) (4) allowing for reduced dosing requirements (reduced from 3 times per day to 2 times per day). A xanthan gum- (b) (4) (b) (4) has been added to the formulation to accomplish these goals. The differences between the original (VIGAMOX) formulation and the Moxifloxacin AF formulation are summarized in Table 1.

Antimicrobial activity and efficacy of Moxifloxacin AF formulation is principally supported, in this Application, by data from three Phase 3 clinical trials, including one active-controlled trial performed in India (Protocol C-04-40) and two vehicle-controlled trials, performed in the U.S. (Protocol C-04-38 and Protocol C-07-40).

Table 1: Comparison of Compositions of Moxifloxacin AF and VIGAMOX

Component	% Composition	
	Moxifloxacin AF	**VIGAMOX**
Moxifloxacin HCl	0.545	Same
Sodium Chloride	(b) (4)	(b) (4)
Xanthan Gum		
Boric Acid		
Sorbitol		
Tyloxapol		
Sodium Hydroxide and/or Hydrochloric Acid	Adjust to pH 7.4	Adjust to pH 6.8
Purified Water	(b) (4)	(b) (4)

Source: This submission, Table 2.3.P.2-1

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].

No new information has been provided, concerning the mechanism of action of moxifloxacin. This Application references information submitted in NDA 21-598 (Vigamox), concerning studies performed to describe the mechanism of action of moxifloxacin.

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].

The Applicant has submitted no "pre-clinical" in vitro antimicrobial data from studies conducted specifically in support of this Application. Data describing the in vitro activity of moxifloxacin against isolates recovered in the clinical trials conducted to support this NDA are used to support the inclusions of specific microorganisms in the Indications section of the proposed label.

The Applicant has submitted summary information from a literature search designed to describe a current antimicrobial profile for moxifloxacin against bacterial isolates included in the "second list" of microorganisms (guidance to clinicians, where only in vitro data are available) in the proposed label for Moxifloxacin AF Ophthalmic Solution, 0.5%. This information is summarized in Tables 1 through 3. Included in the tables are references to summary data from clinical trials discussed in the original submission of this NDA (reference labeled "Alcon Studies 2005 to 2008") and data from Alcon trials used to support NDA 21-598 (VIGAMOX)(Report TDOC-0000208).

Of the referenced studies compiled by the Applicant in support of this NDA or NDA 21-598 (VIGAMOX), most were conducted outside the U.S. Many of the referenced studies were performed at least 10 years prior to this Application. Some studies (e.g. Bauernfeind et al. 1997) did not reference methods approved by (b) (4), and some studies (e.g. FungTomc et al. 2000) did not report quality control procedures. A number of the studies did not investigate a sufficient number of isolates (≥10) to report an MIC_{90} value for a particular species (although several studies reported an MIC_{90} value, nonetheless). Several studies reported non-susceptible values for moxifloxacin against reported pathogens (e.g. Soussy, et al. 2003: moxifloxacin MIC_{90} = 16 mcg/ml against isolates of *Enterococcus faecalis*, n=125).

Table 1: Moxifloxacin Activity against Aerobic Bacteria

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Bacillus anthracis (Total Isolates = 18)							
Bacillus anthracis	18	≤ 0.25	≤0.25-≤0.25	Broth dilution	US	Luna VA et al.	2007
Bacillus cereus (Total Isolates = 91							
Bacillus cereus	11	0.12	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Bacillus cereus	38	0.12	0.032 - 0.25	Broth dilution	US	TDOC-0000208	2003
Bacillus cereus	42	≤ 0.25	≤0.25-≤0.25	Broth dilution	US	Luna VA et al.	2007
Bacillus thuringiensis (Total Isolates = 26)							
Bacillus thuringiensis	7	--	0.06 - 0.25	Broth dilution	US	TDOC-0000208	2003
Bacillus thuringiensis	19	≤ 0.25	≤0.25-≤0.25	Broth dilution	US	Luna VA et al.	2007
Corynebacterium accolens (Total Isolates = 11)							
Corynebacterium accolens	11	0.50	0.015 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium macginleyi (Total Isolates = 38)							
Corynebacterium macginleyi	38	0.12	0.004 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium propinquum (Total Isolates = 29)							
Corynebacterium propinquum	29	0.25	0.25 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium pseudodiphtheriticum (Total Isolates = 95)							
Corynebacterium pseudodiphtheriticum	95	0.25	0.12 – 0.50	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium striatum (Total Isolates = 34)							
Corynebacterium striatum	16	0.12	0.06 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium striatum	18	0.047	0.038 - 8.0	E test	Non-US	Sierra JM et al.	2005
Enterococcus faecalis (Total Isolates = 3357)							
Enterococcus faecalis	79	0.50	0.03 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Enterococcus faecalis	18	0.50	0.25 - 8.0	Agar dilution	US & Non-US	FungTome et al.	2000
Enterococcus faecalis	66	1.0	≤0.5 - 4.0	Agar dilution	Non-US	Del Campo R et al.	2003
Enterococcus faecalis	76	≤0.5	≤0.5 - 4.0	Agar dilution	Non-US	Del Campo R et al.	2003
Enterococcus faecalis	125	16	0.12 - 32	Broth dilution	Non-US	Soussy CJ et al.	2003
Enterococcus faecalis	25	8.0	0.25 - 16	Agar dilution	Non-US	Otani T et al.	2003
Enterococcus faecalis	21	0.5	0.19 - 0.5	E test	Non-US	Pineheiro ET et al.	2004
Enterococcus faecalis	100	1.0	0.12 - 1.0	Agar dilution	Non-US	Bauernfeind et al.	1997
Enterococcus faecalis	30	0.50	0.12 - 4.0	Agar dilution	Non-US	Woodcock et al.	1997
Enterococcus faecalis	2804	0.25	0.03 -16	Broth dilution	Non-US	Schouten et al.	1999
Enterococcus faecalis	13	0.50	0.03 - 8.0	Agar dilution	Non-US	Pong et al.	1999
Kocuria kristinae (Total Isolates = 12)							
Kocuria kristinae	6	--	0.12 – 1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Kocuria kristinae	6	--	0.25 - 0.25	Broth dilution	US	TDOC-0000208	2003
Staphylococcus caprae (Total Isolates = 65)							
Staphylococcus caprae	36	0.12	0.03 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus caprae	29	0.12	0.06 - 0.12	Broth dilution	US	TDOC-0000208	2003
Staphylococcus cohnii (Total Isolates = 35)							
Staphylococcus cohnii	6	--	0.12 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus cohnii	8	--	0.06 - 0.50	Broth dilution	US	TDOC-0000208	2003
Staphylococcus lugdunensis (Total Isolates = 80)							
Staphylococcus cohnii	21	0.06	0.03 - 0.50	Agar dilution	Non-US	Bauernfeind et al.	1997
Staphylococcus lugdunensis	33	0.12	0.06 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus lugdunensis	47	0.25	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Staphylococcus pasteuri (Total Isolates = 32)							
Staphylococcus pasteuri	9	--	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus pasteuri	23	0.25	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Staphylococcus saprophyticus (Total Isolates = 63)							
Staphylococcus saprophyticus	6	--	0.12 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus saprophyticus	27	0.25	0.12 - 0.25	Broth dilution	US	TDOC-0000208	2003

Table 1: Moxifloxacin Activity against Aerobic Bacteria (cont'd)

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Staphylococcus saprophyticus	30	0.25	0.12 - 0.25	Agar dilution	Non-US	Woodcock et al.	1997
Streptococcus agalactiae (Total Isolates = 167)							
Streptococcus agalactiae	18	0.25	0.12 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus agalactiae	10	0.25	0.25 - 0.25	Agar dilution	US & Non-US	FungTome et al.	2000
Streptococcus agalactiae	30	0.25	0.12 - 0.5	Agar dilution	Non-US	King A et al.	2004
Streptococcus agalactiae	26	0.12	0.03 - 0.12	Broth dilution	Non-US	Hoogkamp-Korstanje & Roelofs-Willemse	2000
Streptococcus agalactiae	20	0.25	0.06 - 0.50	Agar dilution	Non-US	Woodcock et al.	1997
Streptococcus agalactiae	38	0.50	0.06 - 0.50	Agar dilution	Non-US	Bauernfeind et al.	1997
Streptococcus agalactiae	25	0.25	0.12 - 0.50	Broth dilution	Non-US	Barry et al.	1999
Streptococcus milleri group (Total Isolates = 79)							
Streptococcus milleri group	79	0.25	0.06 - 0.5	Broth dilution	Non-US	Yamamoto N et al.	2006
Streptococcus mitis (Total Isolates = 241)							
Streptococcus mitis	92	0.25	0.06 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus mitis	94	0.25	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Streptococcus mitis	10	0.12	0.06 - 0.12	Agar dilution	US	Goldstein et al.	2000
Streptococcus mitis	17	0.50	0.12 - 0.50	Agar dilution	US & Non-US	FungTome et al.	2000
Streptococcus mitis	25	0.25	0.06 - 0.25	Broth dilution	Non-US	Hoogkamp-Korstanje & Roelofs-Willemse	2000
Streptococcus mitis	3	0.5	0.12 - 0.5	Broth dilution	Non-US	Presterl E et al.	2005
Streptococcus oralis (Total Isolates = 25)							
Streptococcus oralis	20	0.25	0.12 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus oralis	2	0.12	0.12-0.12	Broth dilution	Non-US	Presterl E et al.	2005
Streptococcus oralis	3	0.25	0.06 - 0.25	Broth dilution	Non-US	Presterl E et al.	2005
Streptococcus parasanguinis (Total = 19)							
Streptococcus parasanguinis	19	0.25	0.12 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus pyogenes (Total Isolates = 642)							
Streptococcus pyogenes	52	0.25	0.12 – 0.50	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus pyogenes	419	0.25	<0.03 - 0.5	Agar dilution	Non-US	Hsueh PR et al.	2003
Streptococcus pyogenes	40	0.12	--	Broth dilution	Non-US	Noviello S et al.	2003
Streptococcus pyogenes	25	0.5	0.12 - 0.5	Agar dilution	Non-US	Otani T et al.	2003
Streptococcus pyogenes	66	0.25	0.06 - 0.5	Broth dilution	Non-US	Liebowitz LD et al.	2003
Streptococcus pyogenes	40	0.25	0.06 - 0.5	Agar dilution	Non-US	King A et al.	2004
Streptococcus salivarius (Total Isolates = 46)							
Streptococcus salivarius	25	0.50	0.06 – 8.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus salivarius	21	0.12	0.06 - 0.25	Broth dilution	US	TDOC-0000208	2003
Streptococcus sanguis (Total Isolates = 11)							
Streptococcus sanguis	9	--	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus sanguis	2	--	0.06 - 0.25	Broth dilution	Non-US	Presterl E et al.	2005
Acinetobacter baumannii (Total Isolates = 164)							
Acinetobacter baumannii	27	0.25	0.03 - 0.50	Broth dilution	US	TDOC-0000208	2003
Acinetobacter baumannii	7	8.0	0.0625 - 8.0	Broth dilution	US	Jung R et al.	2007
Acinetobacter baumannii	18	1.0	0.06 – 2.0	Agar dilution	US & Non-US	FungTome et al.	2000
Acinetobacter baumannii	41	32	0.032 - 64	Broth dilution	Non-US	Soussy CJ et al.	2003
Acinetobacter baumannii	22	1.0	0.25 - 1.0	E test	Non-US	Spence RP et al.	2003
Acinetobacter baumannii	43	0.25	0.008 – 2.0	Agar dilution	Non-US	Bauernfeind et al.	1997
Acinetobacter baumannii	11	2.0	0.008 - 16	Agar dilution	Non-US	Woodcock et al.	1997
Acinetobacter calcoaceticus (Total Isolates = 66)							
Acinetobacter calcoaceticus	13	0.12	0.03 - 64	Agar dilution	US	Higgins et al.	2000
Acinetobacter calcoaceticus	3	--	0.06 - 0.06	Broth dilution	US	TDOC-0000208	2003
Acinetobacter calcoaceticus	30	0.25	<0.003 – 2.0	Agar dilution	Non-US	Dalhoff et al.	1996
Acinetobacter calcoaceticus	20	0.06	0.008 - 0.06	Agar dilution	Non-US	Bauernfeind	1997
Acinetobacter junii (Total Isolates = 33)							
Acinetobacter junii	33	0.12	0.03 - 8.0	Broth dilution	US	TDOC-0000208	2003
Acinetobacter lwoffi (Total Isolates = 9)							
Acinetobacter lwoffi	9	--	0.032 - 0.5	Broth dilution	Non-US	Soussy CJ et al.	2003

Table 1: Moxifloxacin Activity against Aerobic Bacteria (cont'd)

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Acinetobacter schindleri (Total Isolates = 26)							
Acinetobacter schindleri	26	0.06	0.016 - 0.06	Broth dilution	US	TDOC-0000208	2003
Acinetobacter ursingii (Total Isolates = 13)							
Acinetobacter ursingii	13	0.50	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Aeromonas spp. (Total Isolates = 57)							
Aeromonas caviae	9	--	0.03 - 8.0	Broth dilution	US	TDOC-0000208	2003
Aeromonas hydrophila	16	0.12	0.06 - 0.12	Agar dilution	US & Non-US	FungTomc et al.	2000
Aeromonas hydrophila	32	0.03	0.008 - 0.06	Agar dilution	Non-US	Bauernfeind et al.	1997
Chryseobacterium indologenes (Total Isolates = 13)							
Chryseobacterium indologenes	4	--	0303 – 0.06	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Chryseobacterium indologenes	9	--	0.03 - 2.0	Broth dilution	US	TDOC-0000208	2003
Enterobacter aerogenes (Total Isolates = 13)							
Enterobacter aerogenes	7	0.25	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Enterobacter aerogenes	17	0.25	0.03 - 1.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Enterobacter aerogenes	11	0.50	0.12 - 0.50	Broth dilution	US	TDOC-0000208	2003
Enterobacter aerogenes	42	2.0	0.03 - 4.0	Agar dilution	Non-US	Bauernfeind	1997
Enterobacter cloacae (Total Isolates = 108)							
Enterobacter cloacae	27	0.12	0.06-0.50	Broth Dilution	US	Alcon Studies 2005 to 2008	2005 2008
Enterobacter cloacae	63	0.06	0.016 -16	Agar dilution	Non-US	Bauernfeind	1997
Enterobacter cloacae	18	0.25	0.06 - 0.50	Agar dilution	US & Non-US	FungTomc et al.	2000
Haemophilus parainfluenzae (Total Isolates = 34)							
Haemophilus parainfluenzae	23	0.12	0.015 -0.25	Broth dilution	US	Bogdanovich T et al.	2006
Haemophilus parainfluenzae	11	0.12	0.008-0.25	Agar dilution	Non-US	Soussy CJ et al.	2003
Klebsiella oxytoca (Total Isolates = 1668)							
Klebsiella oxytoca	12	0.25	0.06 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Klebsiella oxytoca	44	1.0	0.03 - 16	Agar dilution	Non-US	Soussy CJ et al.	2003
Klebsiella oxytoca	1612	2.0	--	Broth dilution	US & Non-US	Sader HS et al.	2007
Klebsiella oxytoca	1	--	1.0 - 1.0	Agar dilution	Non-US	Lascols C et al.	2007
Moraxella catarrhalis (Total Isolates = 8780)							
Moraxella catarrhalis	127	0.06	0.015 – 0.50	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Moraxella catarrhalis	218	0.06	--	Broth dilution	US	Jacobs MR et al.	2004
Moraxella catarrhalis	5981	0.06	--	Broth dilution	US & Non-US	Jones RN et al.	2007
Moraxella catarrhalis	1656	0.06	--	Broth dilution	US & Non-US	Jones RN et al.	2003
Moraxella catarrhalis	256	0.06	≤0.002 - 0.25	Broth dilution	Non-US	Liebowitz LD et al.	2003
Moraxella catarrhalis	30	0.12	--	Broth dilution	Non-US	Noviello S et al.	2003
Moraxella catarrhalis	85	0.06	≤0.004 - 0.25	Agar dilution	Non-US	Kucukbasmaci et al.	2003
Moraxella catarrhalis	40	0.25	0.016 - 0.25	Agar dilution	Non-US	Soussy CJ et al.	2003
Moraxella catarrhalis	25	0.06	0.03 - 0.12	Agar dilution	Non-US	Otani T et al.	2003
Moraxella catarrhalis	29	0.03	0.015-0.06	Broth dilution	Non-US	Bowker KE et al.	2003
Moraxella catarrhalis	5	0.06	0.062 - 0.062	Broth dilution	Non-US	Drago L et al.	2004
Moraxella catarrhalis	269	0.06	0.03 - 1.0	Agar dilution	Non-US	Morrissey I et al.	2005
Moraxella catarrhalis	46	0.25	0.06 - 8.0	Agar dilution	Non-US	Ling TKW et al.	2005
Moraxella catarrhalis	9	--	0.06 - 0.12	Broth dilution	Non-US	Bogdanovich et al.	2006
Moraxella catarrhalis	40	0.12	≤0.06 - 0.25	Broth dilution	Non-US	Bogdanovich et al.	2006
Moraxella osloensis (Total Isolates = 20)							
Moraxella osloensis	20	0.25	0.03 - 0.25	Broth dilution	US	TDOC-0000208	2003

Table 1: Moxifloxacin Activity against Aerobic Bacteria (cont'd)

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Morganella morganii (Total Isolates = 121)							
Morganella morganii	18	0.50	0.12 - 0.50	Agar dilution	US & Non-US	FungTomc et al.	2000
Morganella morganii	41	0.12	0.03 - 8.0	Agar dilution	Non-US	Bauernfeind	1997
Morganella morganii	15	0.25	0.03 - 0.25	Agar dilution	Non-US	Woodcock et al.	1997
Morganella morganii	47	16	0.063 - 128	Agar dilution	Non-US	Soussy CJ et al.	2003
Neisseria gonorrhoeae (Total Isolates = 240)							
Neisseria gonorrhoeae	34	0.015	0.004 - 0.012	Agar dilution	Non-US	Woodcock et al.	1997
Neisseria gonorrhoeae	31	0.06	0.002 - 0.12	Agar dilution	Non-US	Ruiz J et al.	2003
Neisseria gonorrhoeae, ampicillin^{R}	14	0.03	0.016 - 0.06	Agar dilution	Non-US	Bauernfeind	1997
Neisseria gonorrhoeae, ampicillin^{S}	20	0.016	0.002 - 0.016	Agar dilution	Non-US	Bauernfeind	1997
Neisseria gonorrhoeae, ofloxacin^{S}	23	0.25	≤0.004 - 0.25	Agar dilution	Non-US	Otani T et al.	2003
Neisseria gonorrhoeae, ciprofloxacin^{S}	35	0.03	0.004 - 0.06	Agar dilution	US & Non-US	FungTomc et al.	2000
Neisseria gonorrhoeae, quinolone^{R}	50	0.50	0.06 - 2.0	Agar dilution	US & Non-US	Jones et al.	2000
Neisseria gonorrhoeae, ciprofloxacin^{R}	10	1.0	0.12 - 1.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Neisseria gonorrhoeae, ofloxacin^{R}	23	8.0	1.0 - 8.0	Agar dilution	Non-US	Otani T et al.	2003
Neisseria meningitidis (Total Isolates = 27)							
Neisseria meningitidis	10	0.015	0.004 - 0.015	Agar dilution	Non-US	Woodcock et al.	1997
Neisseria meningitidis	17	0.016	0.008 - 0.016	Agar dilution	US & Non-US	FungTomc et al.	2000
Pantoea agglomerans (Total Isolates = 34)							
Pantoea agglomerans	16	2.0	0.004 – 2.0	Agar dilution	Non-US	Bauernfeind	1997
Pantoea agglomerans	18	0.25	0.03 - 0.25	Broth dilution	US	TDOC-0000208	2003
Proteus vulgaris (Total Isolates = 109)							
Proteus vulgaris	18	1.0	0.06 – 2.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Proteus vulgaris	24	0.25	0.0009 – 4.0	Agar dilution	Non-US	Dalhoff et al.	1996
Proteus vulgaris	15	0.25	0.06 - 0.50	Agar dilution	Non-US	Woodcock et al.	1997
Proteus vulgaris	35	0.50	0.06 - 0.50	Agar dilution	Non-US	Bauernfeind	1997
Proteus vulgaris	17	0.5	0.12 - 1.0	Agar dilution	Non-US	Soussy CJ et al.	2003
Serratia liquefaciens (Total Isolates = 41)							
Serratia liquefaciens	32	1.0	0.03 - 32	Agar dilution	Non-US	Bauernfeind	1997
Serratia liquefaciens	4	2.0	0.03 - 16	Agar dilution	Non-US	Woodcock et al.	1997
Serratia liquefaciens	5	--	0.06 - 0.50	Broth dilution	US	TDOC-0000208	2003
Serratia marcescens (Total Isolates = 177)							
Serratia marcescens	18	1.0	0.25 – 1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Serratia marcescens	33	1.0	0.03 - 2.0	Broth dilution	US	TDOC-0000208	2003
Serratia marcescens	10	0.380	--	E test	US	Kowalski RP et al.	2003
Serratia marcescens	18	0.50	0.06 – 1.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Serratia marcescens	15	2.0	0.03 - 16	Agar dilution	Non-US	Woodcock et al.	1997
Serratia marcescens	61	4.0	0.063 - 16	Agar dilution	Non-US	Soussy CJ et al.	2003
Serratia marcescens	22	2.0	0.25 - 8	Agar dilution	Non-US	Otani T et al.	2003
Stenotrophomonas maltophilia (Total Isolates = 179)							
Stenotrophomonas maltophilia	17	0.50	0.031 - 4.0	Agar dilution	Non-US	Dalhoff et al.	1996
Stenotrophomonas maltophilia	13	2.0	0.06 - 2.0	Agar dilution	Non-US	Woodcock et al.	1997
Stenotrophomonas maltophilia	18	1.0	0.12 - 4.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Stenotrophomonas maltophilia	23	2.0	0.25 - 8.0	Broth dilution	US	TDOC-0000208	2003
Stenotrophomonas maltophilia	47	2.0	≤0.01 - 32	Agar dilution	Non-US	Canton R et al.	2003
Stenotrophomonas maltophilia	38	0.38	0.032 - 16	Broth dilution	Non-US	Soussy CJ et al.	2003
Stenotrophomonas maltophilia	20	4.0	0.12 - 8	Broth dilution	Non-US	Bonaventura et al.	2004
Stenotrophomonas maltophilia	3	--	0.5 - 2.0	Agar dilution	Non-US	Ba BB et al.	2004

Table 2: Moxifloxacin Activity against Anaerobic Bacteria

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Bacteroides vulgatus (Total Isolates=29)							
Bacteroides vulgatus	29	1.0	0.12-32	Broth dilution	US & Non-US	Schaumann et al.	2000
Clostridium perfringens (Total Isolates = 178)							
Clostridium perfringens	40	0.5	0.12 - 2.0	Agar dilution	US	Hecht DW et al.	2003
Clostridium perfringens	18	0.50	0.50 - 0.50	Agar dilution	US & Non-US	FungTome et al.	2000
Clostridium perfringens	11	0.50	0.25 - 0.50	Agar dilution	Not available	Ednie et al.	2002
Clostridium perfringens	20	0.50	Not available	Agar dilution	Not available	Ednie et al.	2002
Clostridium perfringens	25	0.50	0.25 - 1.0	Agar dilution	Non-US	Appelbaum et al.	2002
Clostridium perfringens	8	--	0.12 - 1.0	Agar dilution	Non-US	Soussy CJ et al.	2003
Clostridium perfringens	25	0.5	0.25 - 1.0	Agar dilution	Unknown	Peric M et al.	2004
Peptostreptococcus anaerobius (Total Isolates = 35)							
Peptostreptococcus anaerobius	4	--	0.12-1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus anaerobius	10	8.0	0.25 - 16	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus anaerobius	1	--	0.25 - 0.25	Agar dilution	US	Credito KL et al.	2003
Peptostreptococcus anaerobius	20	0.25	0.12 - 0.25	Agar dilution	US	Ednie L et al.	2007
Peptostreptococcus asacchrolyticus (Total Isolates = 16)							
Peptostreptococcus asacchrolyticus	12	1.0	<=0.25 - 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus asacchrolyticus	1	--	0.12 - 0.25	Agar dilution	US	Credito KL et al.	2003
Peptostreptococcus asacchrolyticus	15	0.25	≤0.015 - 1.0	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus magnus (Total Isolates = 10)							
Peptostreptococcus magnus	10	0.25	0.06 - 0.5	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus micros (Total Isolates = 23)							
Peptostreptococcus micros	11	0.5	<=0.004-0.5	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus micros	12	2.0	0.12 - 4.0	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus prevotii (Total Isolates = 21)							
Peptostreptococcus prevotii	12	1.0	0.12 - 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus prevotii	9	--	0.12 - 1.0	Agar dilution	US	Hecht DW et al.	2003
Porphyromonas gingivalis (Total Isolates = 35)							
Porphyromonas gingivalis	35	0.50	0.06 - 0.50	Broth dilution	Non-US	Milazzo et al.	2002
Porphyromonas spp. (Total Isolates = 11)							
Porphyromonas spp.	11	0.25	≤0.15 - 0.5	Agar dilution	US	Hecht DW et al.	2003
Prevotella buccae (Total Isolates = 43)							
Prevotella buccae	20	1.0	0.5 - 4.0	Agar dilution	US	Ednie L et al.	2007
Prevotella buccae	12	0.5	0.25 - 0.5	Agar dilution	US	Hecht DW et al.	2003
Prevotella buccae	11	0.5	0.25 - 0.5	Agar dilution	Unknown	Peric M et al.	2004
Prevotella corporis (Total Isolates = 12)							
Prevotella corporis	12	1.0	0.5 - 1.0	Agar dilution	Unknown	Peric M et al.	2004
Prevotella melanogenica (Total Isolates = 5)							
Prevotella melanogenica	5	--	0.50 – 1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008

Table 3: Moxifloxacin Activity against Mycobacteria

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Mycobacterium tuberculosis (Total Isolates = 439)							
Mycobacterium tuberculosis	243	0.5	0.06 – 8.0	Agar dilution	Non-US	Rodriguez et al.	2002
Mycobacterium tuberculosis	84	0.5	0.5 - 1.0	Agar dilution	Non-US	Tortoli et al.	2004
Mycobacterium tuberculosis	112	0.5	0.5 – 2.0	Broth dilution	Non-US	Kam et al.	2006
Atypical *Mycobacterium* (169)							
Mycobacterium avium (Total Isolates = 12)							
Mycobacterium avium	12	1.0	<0.25 - 1.0	Broth dilution	Non-US	Gillespie & Billington	1999
Mycobacterium kansasii (Total Isolates =104)							
Mycobacterium kansasii	104	0.12	0.006-1.0	Broth dilution	Non-US	Guna et al.	2005
Mycobacterium marinum (Total Isolates = 53)							
Mycobacterium marinum	53	1.0	0.25 - 4.0	Agar dilution	Non-US	Aubry et al.	2000

The referenced studies show that moxifloxacin is active against a wide variety of pathogens, including those that the Applicant suggests may be potential pathogens in cases of bacterial conjunctivitis, including isolates that are non-susceptible to other quinolones. Recent studies [Ohnsman 2007] suggest that moxifloxacin is also active, in vitro, against isolates most commonly associated with bacterial conjunctivitis, including *Haemophilus influenzae*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Propionibacterium acnes*, although some studies have suggested reduced susceptibility to moxifloxacin in isolates of *S. epidermidis*, due to in gyrA and parC mutations [Betanzos 2009]. Activity of moxifloxacin against these pathogens (pathogens most commonly associated with bacterial conjunctivitis) is also demonstrated in comparisons of isolates collected in clinical trials of VIGAMOX (2001-2002) and isolates collected in the original trials performed to support this Application (2005-2007). These data are summarized in Tables 4 - 7. Of the four species analyzed, only isolates of *S. epidermidis* demonstrated reduced susceptibility to moxifloxacin in the more recent trials.

Table 4: Comparison of Antibiotic Resistance in Ocular Isolates of *Streptococcus pneumoniae*

Streptococcus pneumoniae	**2001-2002**		**2005-2007**	
Total Isolates	**N =159**	**% Resistant**	**N =53**	**% Resistant**
Antibiotic (resistance breakpoint)				
Penicillin-resistant (>0.5 µg/ml)	11	6.9%	1	1.9%
Erythromycin-resistant (>0.5 µg/ml)	53	33%	9	17%
Clindamycin-resistant (>1.0 µg/ml)	9	5.7%	0	0.0%
Tetracycline-resistant (>2.0 µg/ml)	36	23%	3	5.7%
Trimethoprim-resistant (>8.0 µg/ml)	54	34%	7	13%
Sulfamethoxazole-resistant (>128 µg/ml)	73	46%	9	17%
Ciprofloxacin-resistant (>2.0 µg/ml)	1	0.6%	0	0.0%
Moxifloxacin-resistant (>2.0 µg/ml)	0	0.0%	0	0.0%
Moxifloxacin-resistant (>0.5 µg/ml)	0	0.0%	0	0.0%

Source: Table 2.7.2.4.-5; this submission

Table 5: Comparison of Antibiotic Resistance in Ocular Isolates of *Haemophilus influenzae*

Haemophilus influenzae	**2001-2002**		**2005-2007**	
Total Isolates	**N =214**	**% Resistant**	**N =117**	**% Resistant**
Antibiotic (resistance breakpoint)				
Ampicillin-resistant (>2.0 µg/ml)	83	39%	38	33%
Tetracycline-resistant (>4.0 µg/ml)	1	0.5%	2	1.7%
Trimethoprim-resistant (>16 µg/ml)	69	32%	27	23%
Ciprofloxacin-resistant (>0.13 µg/ml)	1	0.5%	0	0.0%
Moxifloxacin-resistant (>0.25 µg/ml)	0	0.0%	0	0.0%

Source: Table 2.7.2.4.-6; this submission

Table 6: Comparison of Antibiotic Resistance in Ocular Isolates of *Staphylococcus aureus*

Staphylococcus aureus	**2001-2002**		**2005-2007**	
Total Isolates	**N = 122**	**% Resistant**	**N = 21**	**% Resistant**
Antibiotic (resistance breakpoint)				
Oxacillin-resistant (>2μg/ml)	14	12%	2	9.5%
Erythromycin-resistant (>2.0 μg/ml)	31	25%	9	43%
Clindamycin-resistant (>1.0 μg/ml)	9	7.4%	1	4.8%
Tobramycin-resistant (>2.0 μg/ml)	19	16%	0	0.0%
Gentamicin-resistant (>2.0 μg/ml)	8	6.6%	0	0.0%
Neomycin-resistant (>8.0 μg/ml)	18	15%	3	14%
Tetracycline-resistant (>2.0 μg/ml)	8	6.6%	1	4.8%
Trimethoprim-resistant (>8.0 μg/ml)	24	20%	1	4.8%
Sulfamethoxazole-resistant (>128 μg/ml)	93	76%	16	76%
Ciprofloxacin-resistant (>2.0 μg/ml)	20	16.4%	1	4.8%
Moxifloxacin-resistant (>2.0 μg/ml)	11	9.0%	1	4.8%
Moxifloxacin-resistant (>0.5 μg/ml)	20	16%	1	4.8%

Source: Table 2.7.2.4.-7; this submission

Table 7: Comparison of Antibiotic Resistance in Ocular Isolates of *Staphylococcus epidermidis*

Staphylococcus epidermidis	**2001-2002**		**2005-2007**	
Total Isolates	**N = 248**	**% Resistant**	**N =65**	**% Resistant**
Antibiotic (resistance breakpoint)				
Oxacillinresistant (>0.25μg/ml)	132	53%	32	49%
Erythromycin-resistant (>2.0 μg/ml)	164	66%	37	57%
Clindamycin-resistant (>1.0 μg/ml)	37	15%	13	20%
Tobramycin-resistant (>2.0 μg/ml)	48	19%	10	15%
Gentamicin-resistant (>2.0 μg/ml)	19	7.7%	3	4.6%
Neomycin-resistant (>4.0 μg/ml)	34	14%	8	12%
Tetracycline-resistant (>2.0 μg/ml)	37	15%	12	19%
Trimethoprim-resistant (>8.0 μg/ml)	32	13%	7	11%
Sulfamethoxazole-resistant (>128 μg/ml)	229	92%	52	80%
Ciprofloxacin-resistant (>2.0 μg/ml)	25	10%	11	17%
Moxifloxacin-resistant (>2.0 μg/ml)	4	1.6%	3	4.6%
Moxifloxacin-resistant (≥0.5 μg/ml)	25	10%	11	17%

Source: Table 2.7.2.4.-8; this submission

Data regarding moxifloxacin activity against isolates commonly associated with bacterial conjunctivitis, recovered from Study Eyes at the baseline visit in the three Phase 3 clinical trials, is summarized in Table 8. Although MIC_{90} values against all of the principle pathogens indicates activity of moxifloxacin in vitro (no data is available for *Chlamydia trachomatis*), the calculated MIC range for isolates of *Staphylococcu*s species suggests a proportion of isolates with reduced susceptibility to the antimicrobial.

Table 8: Moxifloxacin in vitro activity against pre-therapy isolates collected in Phase 3 Clinical Trials (Study Eye, MBITT population) (MIC values expressed as mcg/ml)

Organism	Study C-04-38			Study-04-40			Study 07-40		
	n	MIC_{range}	MIC_{90}	n	MIC_{range}	MIC_{90}	n	MIC_{range}	MIC_{90}
Staphylococcus aureus	11	0.03-0.12	0.06	14	0.03-2	2	27	0.015-64	4
Staphylococcus epidermidis	34	0.06-8	1	51	0.03-32	1	140	≤0.004-32	0.12
Streptococcus pneumoniae	36	0.015-0.12	0.12	0	n/a	n/a	33	0.03-0.25	0.12
Haemophilus influenzae	59	≤0.004-0.06	0.03	0	n/a	n/a	84	0.015-0.06	0.03
Propionibacterium acnes	71	≤0.002-0.125 (2)	0.064 (2)	5	n/a(1)	n/a(1)	187	≤0.12-1 (2)	0.5 (2)
Chlamydia trachomatis	0	n/a	n/a	16	n/a(1)	n/a(1)	0	n/a	n/a

Sources: Document TDOC-0008134, Table 4.9.-1; TDOC-0008133, Table 4.9.-1; this submission, TDOC-0011285, Table 4.8.-1

Notes: (1) susceptibility testing not performed, (2) test performed by (b) (4)-approved agar dilution method (all other susceptibility testing performed by (b) (4)-approved broth-dilution method

The Applicant has submitted no new information regarding the bactericidal activity of moxifloxacin and no new studies of time-kill kinetics against ophthalmologic pathogens. The Applicant has referenced NDA 21-598 with regard to these studies of moxifloxacin ophthalmic solution.

The concentration of moxifloxacin in Moxifloxacin AF Ophthalmic Solution is 5 mg/mL. At the recommended dose (0.50 mg moxifloxacin in 2 drops) initial exposure of the antibiotic is in significant excess, compared to the MIC_{range} of all pathogens listed in the proposed label.

In Summary:

Moxifloxacin is active, in vitro, against a wide variety of bacterial pathogens, including Gram-positive and Gram-negative bacteria, certain obligate anaerobes, and some mycobacterial species. Moxifloxacin in vitro antibacterial activity includes some isolates resistant to other fluoroquinolones (e.g. ciprofloxacin). Summary data compiled by the Applicant to support a list of potential ophthalmic pathogens with in vitro susceptibility to moxifloxacin ("second list" organisms), included only those species with moxifloxacin MIC_{90} values ≤ 2 mcg/ml, and only those species not sufficiently characterized in data compiled from the two large clinical trials. Moxifloxacin was active against pre-therapy isolates of the principle pathogens associated with bacterial conjunctivitis, collected during Phase 3 clinical trials, including isolates of *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *H. influenzae*, and *P. acnes*. Reduced moxifloxacin activity was noted in some staphylococcal isolates. The concentration of moxifloxacin in Moxifloxacin AF Ophthalmic Solution is 5 mg/mL. At the recommended dose (0.50 mg moxifloxacin in 2 drops) initial exposure of the antibiotic is in significant excess, compared to the MIC_{range} of all pathogens listed in the proposed label.

Antimicrobial Spectrum of Activity Studies ~ Conclusions:

Moxifloxacin demonstrates in vitro activity against the primary pathogens associated with bacterial conjunctivitis and against a wide variety of other bacteria that may represent potential ophthalmic pathogens, including some isolates that are non-susceptible to other fluoroquinolones. In vitro testing of these species, both during the Phase 3 trials reported in this Application and as reported in supportive data submitted by the Applicant, supports the inclusion of the species requested in the proposed label.

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 submitted no new information regarding mechanisms of moxifloxacin resistance or the development of moxifloxacin-resistance in bacterial isolates commonly associated with conjunctival infections.

No development of resistance to moxifloxacin was noted in the three Phase 3 clinical trials.

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*.

Resistance Studies ~ Conclusions:

The Applicant has submitted no new information regarding the mechanisms of resistance to moxifloxacin among isolates commonly associated with bacterial conjunctivitis. Recent studies, including literature surveys compiled by the Applicant, suggest decreased susceptibility to moxifloxacin in certain bacterial species, including *Staphylococcus epidermidis* and some *Corynebacterium* species. No development of resistance to moxifloxacin was noted in the three clinical trials of Moxifloxacin AF Ophthalmic Solution.

HUMAN AND ANIMAL STUDIES

ANIMAL EFFICACY STUDIES

In the original submission of NDA 22428, the Applicant submitted data from a study designed to investigate the in vivo activity of Moxifloxacin AF against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Report TDOC-00200; Evaluation of Moxifloxacin Formulations for the Treatment and Prevention of Experimental Bacterial Keratitis). The study, conducted at the Louisiana State University Health Sciences Center (New Orleans, LA) in 2004, tested three formulations of moxifloxacin (VIGAMOX, moxifloxacin with xanthan, and moxifloxacin ointment) in animal models of *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections, including both prophylactic and therapeutic models. Levofloxacin and CILOXAN were included as comparators.

In these experiments, bacteria were grown overnight in nutrient broth, subcultured and incubated until an approximate 10^8 CFU /ml inoculum was prepared. Bacterial density was determined by subculture to sold media. New Zealand White rabbits were intrastromally injected with 10 mcl of the log-phase bacterial culture, and were topically treated. Bacterial load was determined by dissection of corneas, homogenation in sterile phosphate buffered saline, and inoculation to solid media. Tested isolates included *S. aureus* MCC30155 (resistant to ciprofloxacin and oxacillin), *S. aureus* strain 8325-4, and *P. aeruginosa* ATCC 27853. The MIC values for the tested bacteria are summarized in Table 9. Topical treatments (as drops) contained 50 uL of antibiotic solution, equivalent to 0.25 mg moxifloxacin.

Table 9: Minimal Inhibitory Concentration (MIC) of Antibiotics Used in Keratitis Studies

Bacteria	Minimal Inhibitory Concentration (µg/ml)				
	Oxacillin	Ciprofloxacin	Ofloxacin	Levofloxacin	Moxifloxacin
***S. aureus* 8325-4**	Sensitive	0.13	0.25	0.13	0.03
***S. aureus* 30155**	64	128	32	8.0	2.0
***P. aeruginosa* 27853**	N/A	0.13	1.0	0.5	1.0

Source: This submission; Report TDOC-00200, Table 3.2.-1

The results of the investigations are summarized in Tables 10 through 12.

In the early therapy studies (log growth phase), Moxifloxacin AF was more effective than VIGAMOX at decreasing the load of the quinolone-susceptible *S. aureus* strain, and comparable to all comparators against the quinolone-resistant *S. aureus* strain. In the late therapy studies (stationary phase), Moxifloxacin AF was comparable to all moxifloxacin preparations, but more effective than levofloxacin. Against *P. aeruginosa* (treated every hour from 24 to 26 hours, 3 drops total), Moxifloxacin AF treatment was similar to other moxifloxacin preparations in reducing corneal bacterial load, but significantly less active than linezolid.

Table 10: Early (4-9 hours PI) therapy of *S. aureus* keratitis

Antibiotic Formulation	Experiment #1		Experiment #2	
	Log CFU/Cornea	Log Reduction [a]	Log CFU/Cornea	Log Reduction [a]
VIGAMOX (0.5%)	2.35 ± 0.75 [c]	4.65	1.14 ± 0.75 [f]	5.91
Moxifloxacin AF (0.5%)	0.00 ± 0.00 [c, d]	7.00	1.80 ± 0.74 [f]	5.25
Moxifloxacin Ointment (0.5%)	1.10 ± 0.70 [d]	5.90	0.90 ± 0.57 [f]	6.15
Levofloxacin (1.5%)	1.15 ± 1.15 [d]	5.85	1.40 ± 0.76 [f]	6.01
Untreated	7.00 ± 0.26 [b]	--	7.05 ± 0.24 [e]	--

[a] Reduction in log CFU/cornea relative to the untreated group.
[b] Significantly different than all antibiotic-treated groups ($P \leq 0.0004$).
[c] Significantly different from each other ($P = 0.0382$).
[d] Not significantly different than each other ($P = 0.2642$).
[e] Significantly different than all antibiotic-treated groups ($P \leq 0.00001$).
[f] Not significantly different than each other ($P = 0.3154$).
Source: This submission; Report TDOC-00200, Table 4.1.-1

Table 11: Late (10-15 hours PI) therapy of *S. aureus* keratitis

Antibiotic Formulation	10-15 hrs PI	
	Log CFU/Cornea	Log Reduction [a]
VIGAMOX (0.5%)	6.29 ± 0.17 [b]	0.82
Moxifloxacin AF (0.5%)	6.00 ± 0.22 [b]	1.11
Moxifloxacin Ointment (0.5%)	6.46 ± 0.08 [b]	0.65
Levofloxacin (1.5%)	6.52 ± 0.20 [c]	0.59
Untreated	7.11 ± 0.27	--

[a] Reduction in log CFU/cornea relative to the untreated group.
[b] Significantly different than the untreated group ($P \leq 0.0445$).
[c] Not significantly different than the untreated group ($P = 0.0721$).
Source: This submission; Report TDOC-00200, Table 4.1.-2

Table 12: Treatment of *Pseudomonas aeruginosa* Keratitis

Antibiotic Formulation	Log CFU/Cornea	Log Reduction [a]
VIGAMOX (0.5%)	5.78 ± 0.27 [e, f, g]	1.85
Moxifloxacin AF (0.5%)	5.23 ± 0.36 [e, f, g]	2.40
Moxifloxacin Ointment (0.5%)	6.20 ± 0.30 [d, e]	1.43
Levofloxacin (1.5%)	2.41 ± 0.49 [c]	5.22
CILOXAN (0.3%)	5.02 ± 0.37 [d, f]	2.61
Untreated	7.63 ± 0.05 [b]	--

[a] Reduction in log CFU/cornea relative to the untreated group.
[b] Significantly different than antibiotic-treated groups ($P \leq 0.0063$).
[c] Significantly lower than all other groups ($P \leq 0.0001$).
[d] Significantly different from each other ($P = 0.02$).
[e] Moxifloxacin ointment group was not significantly different from the groups treated with VIGAMOX ($P = 0.3789$) or moxifloxacin AF ($P = 0.0503$).
[f] Not significantly different from each other ($P \geq 0.1147$).
[g] Not significantly different from each other ($P = 0.2453$).
Source: This submission; Report TDOC-00200, Table 4.2.-1

In the prophylaxis models (Tables 13 and 14), Moxifloxacin AF was more effective than levofloxacin at limiting growth of *S. aureus* 30155 (resistant to quinolones) when animals were treated 30 minutes prior to bacterial injection, but similar to levofloxacin (and all comparators) when treatment was at 3 hours prior to injection. Against *S. aureus* 8325-4 (susceptible to quinolones), Moxifloxacin AF was more effective as a prophylactic treatment than levofloxacin but statistically similar to other moxifloxacin preparations. Against *P. aeruginosa,* treated 3 hours prior to bacterial injection, Moxifloxacin AF was more effective than VIGAMOX, but less effective than CILOXAN and levofloxacin.

Table 13: Prophylactic treatment of *S. aureus* keratitis

Antibiotic Formulation	Log CFU/Cornea		
	S. aureus 30155		*S. aureus* 8325-4
	30 min [a]	3 hours [a]	8 hours [a]
VIGAMOX (0.5%)	2.95 ± 0.33 [b]	5.41 ± 0.18 [b]	3.33 ± 1.06 [b, g]
Moxifloxacin AF (0.5%)	2.35 ± 0.28 [b]	5.03 ± 0.15 [b]	2.12 ± 1.01 [b, e, g]
Moxifloxacin Ointment (0.5%)	2.58 ± 0.38 [b]	5.19 ± 0.09 [b]	2.89 ± 1.06 [b, e, g]
Levofloxacin (1.5%)	4.89 ± 0.20 [c]	5.09 ± 0.17 [b]	4.69 ± 0.33 [f, g]
Untreated	5.02 ± 0.19 [c, d]	5.00 ± 0.13 [b]	5.73 ± 0.11 [d, f]

[a] Time prior to injection of bacterial inoculum.
[b] No significant difference between groups ($P \geq 0.0550$).
[c] Not significantly different for each other ($P \geq 0.05$)
[d] Significantly different than the antibiotic-treated groups ($P \leq 0.010$).
[e] Significantly different from each other ($P \leq 0.030$).
[f] Not significantly different from each other ($P = 0.2265$).
[g] Significantly different from each other ($P \geq 0.045$).
Source: This submission; Report TDOC-00200, Table 4.3.-1

Table 14: Prophylactic treatment of *P. aeruginosa* Keratitis

Antibiotic Formulation	Log CFU/Cornea
	3 hours [a]
VIGAMOX (0.5%)	5.20 ± 0.14 [c, e, f]
Moxifloxacin AF (0.5%)	4.26 ± 0.41 [b, f, g]
Moxifloxacin Ointment (0.5%)	5.03 ± 0.13 [c, , e, g]
Levofloxacin (1.5%)	2.52 ± 0.40 [b ,d, f]
CILOXAN (0.3%)	2.50 ± 0.43 [b, d, f]
Untreated	5.17 ± 0.21 [b, c]

[a] Time prior to injection of bacterial inoculum.
[b] Untreated group was significantly higher than moxifloxacin AF, levofloxacin (1.5%), and CILOXAN groups ($P \leq 0.0252$).
[c] Not significantly different from each other ($P \geq 0.7076$).
[d] Not significantly different from each other ($P = 0.9512$), but were significantly different from all other groups ($P \leq 0.0002$).
[e] Not significantly different from each other ($P = 0.6629$).
[f] Moxifloxacin AF was significantly different from the CILOXAN, levofloxacin (1.5%), and VIGAMOX groups ($P \leq 0.0221$).
[g] Not significantly different from each other ($P = 0.0541$).
Source: This submission; Report TDOC-00200, Table 4.3.-2

In summary:

The Applicant has submitted a report (TDOC-00200) from a study designed to investigate the in vivo efficacy of Moxifloxacin AF Ophthalmic Solution, compared to VIGAMOX, levofloxacin, and CILOXAN (only used as a comparator in tests against *Pseudomonas aeruginosa*). The studies suggest that Moxifloxacin AF is more effective in early therapy treatment than VIGAMOX against *S. aureus* isolates susceptible to quinolones, similar to VIGAMOX but more effective than levofloxacin against *S. aureus* in late stage therapy models. No statistical difference was noted between comparators in treating isolates of quinolone-resistant *S. aureus* in early stage models. Against *Pseudomonas aeruginosa*, all moxifloxacin preparations were similarly effective, and all were less effective than levofloxacin. In prophylaxis models, all moxifloxacin preparations behaved similarly against *S. aureus* infection in both 30-minute and 3-hour pre-infection treatment regimens. Against *P. aeruginosa*, Moxifloxacin AF prophylaxis was more effective than VIGAMOX, but less effective than levofloxacin or CILOXAN.

Animal Efficacy Studies ~ Conclusions:

Moxifloxacin AF is effective at reducing bacterial counts (quinolone-susceptible and –resistant *S. aureus*, and *P. aeruginosa*), relative to untreated controls, in the corneas of New Zealand white rabbits, in both late- and early-stage therapy. Moxifloxacin AF is also effective, relative to untreated controls, when administered prior to infection (prophylactically) at 30 minutes pre-infection with quinolone-susceptible *S. aureus*, 8 hours pre-infection with quinolone-resistant *S. aureus,* and 3 hours pre-infection with *P. aeruginosa*. Moxifloxacin was statistically similar to the untreated control in a prophylaxis administered 3 hours prior to infection with quinolone-susceptible *S. aureus*.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

In the original submission of NDA 22428, the Applicant submitted data from two studies designed to investigate the pharmacokinetics of Moxifloxacin AF Ophthalmic Solution in tear film and aqueous humor.

In the first experiment (Alcon Report EM:005:00735:1104), tear film concentrations of Moxifloxacin AF were compared to concentrations of VIGAMOX in New Zealand white rabbits. Samples were taken at 1, 5, 10, 30, and 60 after a single dose. Tear film concentrations of Moxifloxacin AF were higher at all sampling points, but only marginally higher in the 60 minute sample (difference decreasing over time) (Table 15). The Applicant determined AUC values for both treatments. The $AUC_{0\text{-}10\ min}$ was significantly higher for Moxifloxacin AF than VIGAMOX (Table 16).

Table 15: Mean concentration ± SD of moxifloxacin in tear film following administration of Moxifloxacin AF Ophthalmic Solution or VIGAMOX®

Test article	Sampling time (min)	Concentration (µg/mL)
Moxifloxacin AF Ophthalmic Solution	1	3656 ± 1292
	5	2035 ± 273
	10	122 ± 120
	30	13.59 ± 9.17
	60	4.98 ± 3.99
VIGAMOX®	1	3621 ± 1000
	5	258 ± 153
	10	17.8 ± 9.1
	30	3.56 ± 2.45
	60	3.02 ± 2.82

Source: This submission, Table 2.6.4.10-2

Table 16: $AUC_{0\text{-}60}$ and statistical comparison of moxifloxacin in tear film following administration of Moxifloxacin AF Ophthalmic Solution or VIGAMOX®

Moxifloxacin AF Ophthalmic Solution			**VIGAMOX®**		
$AUC_{0\text{-}60\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}60\ min}$)	dfSE ($AUC_{0\text{-}60\ min}$)	$AUC_{0\text{-}60\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}60\ min}$)	dfSE ($AUC_{0\text{-}60\ min}$)
20240	1376	13	10571	1161	5
df dif Moxifloxacin AF - VIGAMOX® = 16			$t = 5{,}371$	$p<0.01$	

SE = standard error
df = degrees of freedom

Source: This submission, Table 2.6.4.10-3

In the second study (Alcon Report EM:002:00735:0804), concentrations of Moxifloxacin AF and VIGAMOX were determined in pigmented New Zealand white rabbit aqueous humor at various sampling points (15, 30, 60, and 120 minutes) following a single dose of antibiotic. Concentrations of Moxifloxacin AF were higher than those of VIGAMOX at all sampling points (Table 17), and the calculated $AUC_{0\text{-}12\ min}$ was statistically higher for the Moxifloxacin AF treated animals (Table 18).

Table 17: Mean concentration ± SD of moxifloxacin in aqueous humor following administration of Moxifloxacin AF Ophthalmic Solution of VIGAMOX®

Test article	Sampling time (min)	Concentration (µg/mL)
Moxifloxacin AF Ophthalmic Solution	15	2.21 ± 0.69
	30	4.74 ± 0.70
	60	2.54 ± 0.77
	120	0.78 ± 0.30
VIGAMOX®	15	0.89 ± 0.37
	30	1.61 ± 0.71
	60	1.18 ± 0.49
	120	0.49 ± 0.03

Source: This submission, Table 2.6.4.10-4

Table 18: AUC0-120 and statistical comparison of moxifloxacin in aqueous humor following administration of Moxifloxacin AF Ophthalmic Solution or VIGAMOX®

Moxifloxacin AF Ophthalmic Solution			**VIGAMOX®**		
$AUC_{0\text{-}120\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}120\ min}$)	dfSE ($AUC_{0\text{-}120\ min}$)	$AUC_{0\text{-}120\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}120\ min}$)	dfSE ($AUC_{0\text{-}120\ min}$)
277	17	9	118	11	10
df dif Moxifloxacin AF - VIGAMOX® = 16			$t = 7.973$	$p<0.01$	

SE = standard error
df = degrees of freedom
Source: This submission, Table 2.6.4.10-5

Study C-05-15 was designed as a single-center, double-masked multi-dose study in healthy subjects to evaluate the steady-state plasma pharmacokinetics of moxifloxacin, following bilateral, topical administration of Moxifloxacin AF Ophthalmic Solution 0.5% in healthy adult subjects. The study enrolled 30 subjects, 20 of whom received that active treatment and 10 of whom received vehicle. Subjects were dosed twice daily (every 12 hours) for four days, and a last dose was administered on the morning of Day 5. Plasma samples were collected prior to the morning dose on Days 2 through 5. Serial samples were collected on Day 5 (0.25, 0.5,1,2,4,6,8,12 hours), on Day 6 (at 24 hours after last dose), and Day 7 (48 hours after last dose).

Mean peak moxifloxacin concentration was observed after one hour, and mean steady-state concentrations were achieved by Day 3. At C_{max}, plasma levels of Moxifloxacin AF Ophthalmic Solution were significantly lower than that of VIGAMOX (0.977 ng/ml, and 2.70 ng/ml, respectively). Data from Study C-05-15 are summarized in Table 19.

Table 19: Moxifloxacin steady-state plasma pharmacokinetic parameters after administration of Moxifloxacin AF Ophthalmic Solution (two times a day) and VIGAMOX® (three times a day)

Moxifloxacin AF Ophthalmic Solution BID (C-05-15)					
	C_{max} (ng/mL)	**T_{max} (h)**	**AUC_{0-8} (ng*h/mL)**	**AUC_{0-12} (ng*h/mL)**	**$t_{1/2}$ (h)**
Mean	0.977	0.88	6.08	8.17	16.6
SD	0.673	0.55	4.05	5.31	5.5
Min	0.267	0.25	1.77	2.33	7.6
Max	3.19	2.00	17.7	22.8	27.3
N	20	20	20	20	20
VIGAMOX® TID (C-01-48)					
	C_{max} (ng/mL)	**T_{max} (h)**	**AUC_{0-8} (ng*h/mL)**	**AUC_{0-12} (ng*h/mL)**	**$t_{1/2}$ (h)**
Mean	2.70	0.57	15.0	ND	13.1
SD	1.29	0.40	5.3	ND	3.3
Min	0.98	0.23	8.1	ND	7.0
Max	5.95	2.00	25.1	ND	19.7
N	21	21	19	ND	19

ND = Not determined
Source: This submission, Table 2.7.2.3.-1

(b) (4)

Table 20: Descriptive Statistics for the Moxifloxacin Conjunctival Tissue Concentrations (ng/g) After a Single Topical Ocular Dose of Moxifloxacin AF Ophthalmic Solution 0.5% or VIGAMOX in Cataract Surgery Patients (Excluding Patients with Low Conjunctival Biopsy Weights)

Treatment	Time Point (h)	Moxifloxacin Conjunctival Tissue Concentration (ng/g) Mean	Median	SD	SE	N	Min	Max	p-value*
Moxifloxacin AF	0.25	43820	25050	49220	14209	12	1050	181000	0.1777
	0.5	35490	26100	31787	8816	13	135	105000	0.4135
	1	19256	18000	16370	4540	13	331	48600	0.0456
	3	2215	1795	1755	507	12	175	6250	0.4276
	5	1847	1580	1407	424	11	151	4760	0.2195
VIGAMOX	0.25	22269	18350	18615	5374	12	257	58000	
	0.5	24112	9030	35071	10574	11	309	101000	
	1	8599	9130	6819	1891	13	131	21200	
	3	1726	1440	1246	346	13	130	3935	
	5	1160	693	1198	346	12	75.0	3335	

Moxifloxacin AF = Moxifloxacin Alternative Formula Ophthalmic Solution 0.5%
VIGAMOX = Moxifloxacin Hydrochloride Ophthalmic Solution 0.5%
* t-test performed at each time point; p-value from two-sample t-test
Individual BLQ values replaced with one-half the limit of quantitation
Source: This submission, Table 2.7.2.2.1.-1

Table 21: Comparison of Moxifloxacin Conjunctival AUCO-3 (h*ng/g) After a Single Topical Ocular Dose of Moxifloxacin AF Ophthalmic Solution 0.5% or VIGAMOX in Cataract Surgery Patients (Excluding Patients with Low Conjunctival Biopsy Weights)

Moxifloxacin AF AUC_{0-3}*	VIGAMOX $AUC_{(0-3)}$ *	Difference	p-value[1]
50548	27084	-23464	0.0115

Moxifloxacin AF = Moxifloxacin Alternative Formula Ophthalmic Solution 0.5%
VIGAMOX = Moxifloxacin Hydrochloride Ophthalmic Solution 0.5%
* A mean concentration of 0 ng/g was imputed at time 0 for each treatment group to obtain the estimates of AUC_{0-3}
[1] p-value based on a t-test of AUCs derived using Bailer's method
BLQ values replaced with one-half the limit of quantitation
Source: This submission, Table 2.7.2.2.1.-2

In summary:

In a study designed to investigate the concentration of Moxifloxacin AF in tear film, New Zealand white rabbits were dosed once with Moxifloxacin AF or VIGAMOX. Moxifloxacin AF concentrations exceeded those of VIGAMOX at all sampling times, although the difference decreased over time. $AUC_{0-16\ min}$ for Moxifloxacin AF was significantly higher than that of VIGAMOX. Similarly, in a study designed to investigate the concentration of Moxifloxacin AF in the aqueous humor of New Zealand white rabbits, following a single administration, Moxifloxacin AF concentration exceeded that of VIGAMOX at each sampling point. $AUC_{0-120\ min}$ was significantly higher for the Moxifloxacin AF-treated animals than for the VIGAMOX-treated group. Results from Study C-05-15 (a Phase 1 clinical trial, enrolling 30 subjects) indicate rapid absorption of moxifloxacin, with C_{max} (0.977 ng/ml) attained within one hour of dosing. Steady-state concentrations were attained by Day 3 of a twice-daily (every 12 hours) dosing regimen. Systemic exposure over the 12-hour dosing interval (AUC_{0-12}) averaged 8.17 ± 5.31 ng*h/mL. Results from Study C-07-12 indicated that the higher conjunctival concentrations of moxifloxacin were achieved more rapidly in patients treated with Moxifloxacin AF (T_{max} = 0.25 hours, C_{max} = 43820 ± 49220 ng/g) compared to patients treated with VIGAMOX (T_{max} = 0.5 hours, C_{max} = 24112 ± 35071 ng/g), and that conjunctiva AUC_{0-3} was significantly higher in patients treated with Moxifloxacin AF, compared to those treated with VIGAMOX (50548 h*ng/g and 27084 h*ng/g, respectively).

Pharmacokinetic / Pharmacodynamic Studies ~ Conclusions:

Experiments in New Zealand white rabbits suggest that Moxifloxacin AF attains high concentrations in both tear film and aqueous humor following a single dose of the antimicrobial, and that levels in both fluids exceed those of VIGAMOX administered identically. Clinical trials in healthy human subjects suggest that Moxifloxacin AF administration over a dosing interval results in lower systemic exposure compared to that of VIGAMOX. Clinical trials in patients undergoing cataract surgery suggest that higher concentrations of moxifloxacin in conjunctival tissue are achieved more rapidly in patients receiving Moxifloxacin AF therapy, compared to those receiving VIGAMOX therapy, and that drug exposure, measured as AUC_{0-3}, is higher in Moxifloxacin AF-treated patients.

CLINICAL TRIALS

The Applicant conducted three Phase 3 trials in support of this NDA. The clinical trials were designed as prospective, multicenter, double-masked, parallel group studies. Studies C-04-38 and C-07-40 were conducted in the U.S. and were designed to demonstrate superiority over vehicle. Subjects received a three-day course of either one drop of Moxifloxacin AF Ophthalmic Solution two times a day in both eyes, or one drop of vehicle two times per day in both eyes. Study C-04-40 was conducted in India and was designed to demonstrate non-inferiority to VIGAMOX. Subjects received a three-day course of either one drop of Moxifloxacin two times per day in both eyes (and one drop of vehicle in both eyes, delivered mid-day, to protect masking), or one drop of VIGAMOX three time per day in both eyes.

Participants included subjects one month of age or older with a diagnosis of bacterial conjunctivitis based on clinical observation. The major exclusion and inclusion criteria were similar for all trials.

For studies C-04-38 and C-04-40, the principle evaluation visits included a Baseline Visit (Day 1), an End of Therapy Visit (Day 4, 12-48 hours after last dose), and a Test of Cure Visit (Day 7, 60-96 hours after last dose). The primary efficacy endpoints for both studies were clinical cure (complete resolution bulbar conjunctival injection and conjunctival discharge/exudate) and microbiological success (eradication of all pathogens identified at the Baseline Visit). Microbiological samples were collected at Day 1 and Day 7.

For study C-07-40, the principle evaluation visits included a Baseline Visit (Day 1) and the End of Therapy Visit (Day 4, 12-48 hours after last dose). The primary efficacy endpoint was clinical cure. Microbiological success was evaluated as a secondary variable. Microbiological samples were collected at Day 1 and Day 4.

"Microbiology treatment failure" was defined as any one of the following, 1) persistence of the pre-therapy pathogen(s), or presumed persistence if no specimen is collected in a patient with clinical signs; 2) reinfection (recovery of a pathogen at the Test of Cure Visit that was not present at the Baseline Visit), and 3) early discontinuation due to treatment failure (regardless of specimen culture results).

The study parameters for C-07-40, C-04-48 and C-04-40 are summarized in Table 22.

Table 22: Study Parameters for C-07-40, C-04-38 and C-04-40

Study	C-07-40	C-04-38	C-04-40
Location	U.S.		India
Statistical Objective	Demonstrate superiority of Moxifloxacin AF to Vehicle for the treatment of bacterial conjunctivitis		Demonstrate noninferiority of Moxifloxacin AF to VIGAMOX for the treatment of bacterial conjunctivitis
Treatment Groups	1) Moxifloxacin AF Ophthalmic Solution 2) Vehicle		1) Moxifloxacin AF Ophthalmic Solution 2) VIGAMOX
Dosing Regimen	BID for 3 days		1) Moxifloxacin AF: BID for 3 days (Vehicle dose at mid-day) 2) VIGAMOX: TID for 3 days
Patient Population	Adults and children (≥1 month of age) with bacterial conjunctivitis		
Patient Numbers (Planned)	Approx. 1644 patients to yield a minimum of 822 bacterial pathogen positive patients (411 per study arm)	Approx. 600 patients to yield a minimum of 300 bacterial pathogen positive patients (150 per study arm)	Approx. 675 patients to yield a minimum of 370 bacterial pathogen positive patients (185 per study arm)
Primary Efficacy	**Clinical cure** at the EOT[2] Visit.	**Clinical cure** and **microbiological success** at the TOC[1] Visit.	**Clinical cure** and **microbiological success** at the TOC[1] Visit.
Key Secondary Efficacy	**Microbiological success** at the EOT[2] Visit	N/A	N/A
Secondary Efficacy	Eight individual sign and symptom cure rates: bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing, photophobia at each visit. Clinical cure at the Day 3 Visit.	Eight individual signs and symptoms of bacterial conjunctivitis: bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing, photophobia at each visit.	Eight individual signs and symptoms of bacterial conjunctivitis: bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing, photophobia at each visit.
Safety Variables	Visual acuity, cornea and iris/anterior chamber, lens (C-07-40 only), dilated fundus exam, adverse events		
Study Visits	Day 1 (Baseline/Screening); Day 3; Day 4 (EOT[2]: 12-48 hrs after last dose)	Day 1 (Baseline/Screening); Day 3; Day 4 (EOT[2]: 12-48 hrs after last dose) Day 7 (TOC[1]: 60-96 hrs after last dose)	Day 1 (Baseline/Screening); Day 3; Day 4 (EOT[2]: 12-48 hrs after last dose) Day 7 (TOC[1]: 60-96 hrs after last dose)
Primary Efficacy Data Set	Microbiological Intent-to-Treat (MBITT)	Modified Intent-to-Treat (MITT)[3]	Modified Per Protocol (MPP)

[1] Test-of-Cure
[2] End-of-Therapy
[3] In C-04-38, the MBITT data set results were requested by the FDA and included in this resubmission.
Source: This submission, Table 2.7.3.1.-1

The primary efficacy data set employed in the analysis for the current submission was the Microbiological Intent-to-Treat (MBITT) data set, defined as all subjects who were pathogen-positive at the screen visit, received at least one dose of study medication, and had at least one on-therapy visit. The study protocols defined six data sets, described in Table 23.

Table 23: Data Set Definitions

Analysis Data Set	Patient-Level Evaluability Criteria					
	Receive Drug	**Pathogen Positive at Day 1**	**At Least One On-Therapy Visit**	**Meet Pre-Randomization Inclusion/ Exclusion Criteria**	**No Major Protocol Violations**	**Baseline and Test-of-Cure/ Exit Data**
Safety	✓					
ITT[1]	✓		✓			
MBITT[a]	✓	✓	✓			
MITT[a]	✓	✓	✓	✓		
PP[b]	✓		✓	✓	✓	✓
MPP[b]	✓	✓	✓	✓	✓	✓

✓ = Criterion must be met to be evaluable.
[a]Patients with no on-therapy data were included as treatment failures. Include imputed values for all missing data including those for patients who were early discontinuations.
[b]Patients in the ITT and MBITT data sets who discontinued early due to treatment failure were included in these per protocol analyses as treatment failures with patient-level outcomes assigned as failure (note that this was the only data imputation performed).
ITT = Intent-to-Treat; MBITT = Microbiological Intent-to-Treat; MITT = Modified Intent-to-Treat;
PP = Per Protocol; MPP = Modified Per Protocol
Source: This submission, Table 2.7.3.1.-2

The hierarchy for defining the study eye is summarized in Table 24.

Table 24: Study Eye Definition

Hierarchical Order for Defining Study Eye	Affected[a] Eye(s)	Pathogen Positive Eye(s)	Study Eye Definition
1	Both	Both	The evaluable eye with the higher score for the cardinal ocular signs[b] at the Day 1 visit
2	Both	One	The pathogen positive eye
3	Both	Neither	The evaluable eye with the higher score for the cardinal ocular signs[b] at the Day 1 visit
4	One	One	The affected eye
5	One	Neither	The affected eye

[a]Affected eye(s) met the pre-therapy inclusion criteria.
[b]If both eyes were rated equally for the two cardinal ocular signs, the right eye was defined as the study eye.
Source: This submission, Table 2.7.3.1.-3

Commercial laboratories were contracted by the Applicant to provide clinical microbiology support. For studies C-04-38 and C-07-40, (b) (4) was the contract microbiology laboratory. For Study C-04-40, (b) (4) was the contract microbiology laboratory. The contract laboratories provided an Investigator Laboratory Manual with instructions for specimen collection, as well as supplies for collection and shipping, to each investigator. The contract laboratories were responsible for specimen processing, identification of microorganisms, susceptibility testing, shipping all recovered isolates to the Applicant for long-term storage, and reporting results to the Applicant.

Specimens were collected using two sterile disposable "mini-tip" Dacron swabs, one for bacterial culture and the other for adenovirus and Chlamydia culture. The swab for bacterial culture was shipped in an anaerobic/aerobic culture transport system. The swab for chlamydial and viral culture was shipped in a dry sheath. Swabs for bacterial cultured were plated to appropriate media for growth of aerobic and anaerobic microorganisms. Specimen Gram stains were not performed. Swabs for viral/chlamydial culture were tested using the Qiagen QIAmp DNA Mini Kit for amplification and BioSynthesis Fastype™ kits for identification of adenovirus and/or *Chlamydia trachomatis*. Bacteria were identified using API® test strips (bioMerieux) and/or VITEK® (bioMerieux). Susceptibility testing was performed using the Sensititre® Microbial System (Trek Diagnostics), using panels designed by the Applicant. A list of the tested antimicrobials is presented in Table 25 (Studies C-04-38 and C-04-40) and Table 26 (Study C-07-40). Quality control results were included in the Microbiology Study Report. Persistent pathogens, microorganisms present at Test of Cure visit that were present at the Baseline Visit (pre-therapy), were identified by automated ribotyping, using a Qualicon RiboPrinter. Isolates with identical ribopatterns were considered to be the same infecting strain.

Table 25: Antibiotics for Susceptibility Testing (Studies C-04-38 and C-04-40)

Antibiotic Class	Antibiotic	Range of Antibiotic Concentrations in Alcon Microtiter Broth Dilution Panels (µg/ml)
Fluoroquinolones	Moxifloxacin (Broth Dilution)	0.004 - 8
	Ciprofloxacin	0.002 - 64
	Ofloxacin	0.008 - 64
Aminoglycosides	Tobramycin	0.015 - 256
	Gentamicin	0.015 - 128
	Neomycin	0.015 - 64
B-lactams	Ampicillin	0.008 - 256
	Ampicillin:Sulbactam	0.12 - 64
	Amoxicillin	0.06 - 128
	Cefazolin	0.06 - 256
	Ceftazidime	0.06 - 256
	Oxacillin	0.03 - 64
	Penicillin	0.015 - 256
	Piperacillin	0.012 - 128
Macrolides	Erythromycin	0.016 - 256
Other Antibiotics	Clindamycin	0.015 - 256
	Polymyxin B	0.06 - 64
	Sulfamethaxazole	0.03 - 512
	Tetracycline	0.03 - 128
	Trimethoprim	0.002 - 256

Source: Original submission; Report TDOC-0008133, Table 3.3.2.4.01
Note: Also tested in Study C-0438: Moxifloxacin (Agar Dilution), 0.004-8 mcg/ml and ceftriaxone (anaerobes only), 0.12-0.5 mcg/ml

Table 26: Antibiotics for Susceptibility Testing (Study C-07-40)

Antibiotic Class	Antibiotic	Range of Antibiotic Concentrations Tested[a] (µg/ml)
Fluoroquinolones	Moxifloxacin (aerobic bacteria)	0.004-128 (Broth Dilution)
	*Moxifloxacin (anaerobes only)	0.002-0.5 (Agar Dilution)
	*Ciprofloxacin	0.002-128
	Ofloxacin	0.004-64
Aminoglycosides	*Tobramycin	0.015-1024
	*Gentamicin	0.015-1024
	Neomycin	0.015-64
β-lactams	*Ampicillin	0.008-256
	Ampicillin-Sulbactam (2:1 ratio)	0.12/0.06-64/32
	Amoxicillin	0.06-128
	Cefazolin	0.06-256
	Ceftazidime	0.12-256
	*Ceftizoxime (anaerobes only)	0.002-32 (Etest)
	Imipenem	0.12-64
	Oxacillin	0.03-64
	Penicillin	0.015-256
	Piperacillin	0.12-128
Macrolides	*Erythromycin	0.03-256
Other Antibiotics	Chloramphenicol	0.12-128
	*Clindamycin	0.015-256
	*Minocycline	0.03-64
	Polymyxin B	0.06-64
	Rifampin	0.015-128
	*Sulfamethaxazole	0.03-512
	Tetracycline	0.03-256
	*Trimethoprim	0.06-256
	Vancomycin	0.06-128

Source: This submission; Table 3.3.2.4.-1

The Applicant provided no threshold criteria for determining the pathologic significance of isolated bacteria from eye cultures. No such criteria were included in the protocols or Microbiology Reports for C-04-38 (TDOC-0008133), C-04-40 (TDOC-00008134), or C-07-40 (TDOC-0011285). All bacteria recovered from collection swabs were presumably reported as "pathogens", regardless of species identification and quantity in culture.

All isolates were shipped to the Applicant for cryopreservation and long term storage.

STUDY C-07-40

Study C-07-40 was performed in the U.S., with patients enrolled from October 2008 through March 2010. A total of 1180 subjects were evaluable in the intent-to-treat (ITT) analyses, 847 in the microbiological intent-to-treat (MBITT) analyses (424 in the Moxifloxacin AF arm, 423 in the vehicle arm), 829 in the modified intent-to-treat (MITT) analyses (415 in the Moxifloxacin AF arm, 414 in the vehicle arm), 1068 in the per protocol (PP) analyses (539 in the Moxifloxacin AF arm, 529 in the vehicle arm), and 763 in the modified per protocol (MPP) analyses (383 in the Moxifloxacin AF arm, 380 in the vehicle arm). Demographics were similar in the two arms, with the largest percentage of subjects between 18 and 64 years of age.

The most frequently isolated bacteria from subjects seen in Study C-07-40 were *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Propionibacterium acnes*, *Staphylococcus epidermidis*, *S. capitis*, and *S. aureus*. No *Chlamydia trachomatis* was identified in subjects seen in this study. Adenovirus was identified in 15 subjects (all 15 were also positive for bacteria at Day 1, and were included in the MBITT data set. A total of 1700 isolates were collected from affected eyes from all enrolled patients, at the Day 1 Visit.

Microbiological and clinical cure rates at the Day 4 Visit are summarized in Tables 27 and 28, respectively. In the Moxifloxacin AF treatment group (MBITT population), 74.5% (316 of 424) of subjects were identified as microbiological successes, with complete eradication of all pre-therapy pathogens. In the vehicle group, 56.0% (237 of 423) of subjects were classified as microbiological success). Of the clinical failures in the Moxifloxacin AF treatment arm, 37 of 100 (37%) had persisting pathogens and 63% (63 of 100) were designated as failures due to superinfection. No increased resistance was noted in these isolates.

Eradication rates, based on microbiological success (MBITT dataset) for the principle bacterial species associated with bacterial conjunctivitis that were treated in the Moxifloxacin AF group were:

- 82.8% (24 of 29) *Streptococcus pneumoniae* (compared to 50% (12 of 24) for vehicle)
- 89.2% (99 of 111) *Staphylococcus epidermidis* (compared to 83.5% (76 of 91) for vehicle)
- 95.8% (23 of 24) *S. aureus* (compared to 77.8% (14 of 18) for vehicle)
- 90.0% (27 of 30) *S. capitis* (compared to 82.9% (29 of 35) for vehicle)
- 95.9% (71 of 74) *Haemophilus influenzae* (compared to 56.5% (39 of 69) for vehicle)
- 88.0% (147 of 167) *Propionibacterium acnes* (compared to 82.4% (147 of 167) for vehicle)

Eradication rates based on clinical cure (i.e. eradication of baseline pathogens in patients that were clinical cures) (MBITT dataset) for the principle bacterial species associated with bacterial conjunctivitis that were treated in the Moxifloxacin AF group were:

- 86.4% (19 of 22) *Streptococcus pneumoniae* (compared to 50.0% (9 of 18) for vehicle)
- 90.6% (77 of 85) *Staphylococcus epidermidis* (compared to 86.3% (63 of 73) for vehicle)
- 94.1% (16 of 17) *S. aureus* (compared to 80.0% (12 of 15) for vehicle)
- 94.7% (18 of 19) *S. capitis* (compared to 80.0% (24 of 30) for vehicle)
- 100.0% (60 of 60) *Haemophilus influenzae* (compared to 59.6% (21 of 31) for vehicle)
- 90.4% (113 of 125) *Propionibacterium acnes* (compared to 84.5% (87 of 104) for vehicle)

Table 27: C-07-40, Clinical Cure Rate at the Day 4 (EOT)/Exit Visit by Treatment (MBITT)

	Treatment									
	Moxifloxacin AF Clinical Cure			Vehicle Clinical Cure						
	Total	Yes		Total	Yes					
Data Set	N	N	%	N	N	%	Delta	Lower[a]	Upper[a]	p-Value[b]
MBITT	424	265	62.5	423	214	50.6	11.9	5.3	18.5	0.0005
ITT	593	372	62.7	586	310	52.9	9.8	4.2	15.4	0.0006
MITT	415	261	62.9	414	207	50.0	12.9	6.2	19.6	0.0002
PP	539	342	63.5	529	285	53.9	9.6	3.7	15.5	0.0015
MPP	383	243	63.4	380	194	51.1	12.4	5.4	19.4	0.0005

26 patients had missing bulbar conjunctival injection and/or conjunctival discharge/exudate data at the Day 4 (EOT)/Exit Visit for PP.
23 patients had missing bulbar conjunctival injection and/or conjunctival discharge/exudate data at the Day 4 (EOT)/Exit Visit for MPP.
[a] 95% Confidence Limits for Moxifloxacin AF - Vehicle
[b] Test = Chi-square (Fishers Exact test if N < 5)
Source: This submission; Table 2.7.3.2.-2

Table 28: Microbiological Success Rate at the Day 4 (EOT)/Exit Visit (MBITT)

	Treatment									
	Moxifloxacin AF Micro Success			Vehicle Micro Success						
	Total	Yes		Total	Yes					
Data Set	N	N	%	N	N	%	Delta	Lower[a]	Upper[a]	p-Value[b]
MBITT	424	316	74.5	423	237	56.0	18.5	12.2	24.8	<0.0001
MITT	415	308	74.2	414	231	55.8	18.4	12.0	24.8	<0.0001
MPP	385	285	74.0	384	220	57.3	16.7	10.1	23.3	<0.0001

17 patients had missing microbiological outcomes at the Day 4 (EOT)/Exit Visit for MPP.
[a] 95% Confidence Limits for Moxifloxacin AF - Vehicle
[b] Test = Chi-square (Fishers Exact test if N < 5)
Source: This submission; Table 2.7.3.2.-3

Microbiological success in the MPP data set at EOT ((769 of 814 patients) is summarized in Table 29.

Table 29: Microbiological Success Rate by Treatment Group (MPP)

	Treatment								
	Moxifloxacin AF				Vehicle				
	Microbiological Outcome				Microbiological Outcome				
	Success		Failure		Success		Failure		
Data Set	N	%	N	%	N	%	N	%	p-value[a]
MBITT	316	74.5	108	25.5	237	56.0	186	44.0	<0.0001
MITT	308	74.2	107	25.8	231	55.8	183	44.2	<0.0001
MPP	285	74.0	100	26.0	220	57.3	164	42.7	<0.0001

[a] Chi-square test of independence (or Fisher's Exact test if N<5)
Source: This submission; TDOC-0011285, Table 4.5.2.-1

Of the patients designated microbiological failures in the Moxifloxacin AF arm (MPP data set, 100 patients), 37 were classified as failures due to persistence (i.e. presence of the pre-therapy pathogen was present in the Exit specimen, or presumed persistence if no specimen was collected in a patient with clinical signs) (Table 30), and 63 were classified as failures due to

superinfection (i.e. a new pathogen was present at the Exit Visit in a patient with clinical signs) (Table 31). In the vehicle arm, there were 71 patients with persisting pathogens and 93 patients who were designated as failures due to superinfection.

Table 30: Microbiological Failures Due to Persistence – Moxifloxacin AF Treatment Group (MPP)

Inv	Pt	Organisms Isolated at Pre-therapy	MOX[a] MIC (µg/mL)	Days On Therapy	Failure[b] Day	Organisms Isolated at Time of Failure	MOX[a] MIC (µg/mL)
2678	9106	*Staphylococcus aureus*	0.12	3	5	*Staphylococcus aureus*	0.12
1939	5106	*Streptococcus pneumoniae*	0.06	2	3	None; Presumed Persistance	
3495	551	*Streptococcus pneumoniae*	0.12	3	5	*Streptococcus pneumoniae*	0.12
4131	3120	*Streptococcus pneumoniae*	0.06	3	5	*Streptococcus pneumoniae*	0.12
5094	3202	*Streptococcus pneumoniae* *Staphylococcus epidermidis*	0.06 16	3	4	*Staphylococcus epidermidis* *Propionibacterium acnes*	32 0.094
5412	1807	*Streptococcus pneumoniae* *Propionibacterium acnes* *Staphylococcus capitis*	0.12 0.125 0.12	2	2	None; Presumed Persistance	
5488	6101	*Streptococcus pneumoniae* *Propionibacterium acnes*	0.12 0.094	4	5	*Staphylococcus epidermidis* *Propionibacterium acnes*	0.06 0.125
5494	7438	*Streptococcus pneumoniae* *Moraxella catarrhalis*	0.12 0.03	3	5	*Streptococcus pneumoniae*	0.12
3346	8704	*Haemophilus influenzae*	0.03	3	4	*Haemophilus influenzae* *Staphylococcus epidermidis*	≤0.004 1
3568	9232	*Haemophilus influenzae* *Propionibacterium acnes* *Staphylococcus epidermidis*	0.03 0.125 0.06	3	4	*Propionibacterium acnes* *Staphylococcus capitis*	0.125 0.06
4663	4325	*Haemophilus influenzae*	0.015	3	5	*Haemophilus influenzae*	0.015
2449	4611	*Propionibacterium acnes*	0.094	2	3	None; Presumed Persistance	
3631	140	*Propionibacterium acnes* *Staphylococcus epidermidis* *Acinetobacter* species	0.064 0.06 0.25	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.064 0.06
3851	5503	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.19 0.12	3	4	*Propionibacterium acnes*	0.094
2678	9106	*Staphylococcus aureus*	0.12	3	5	*Staphylococcus aureus*	0.12
1939	5106	*Streptococcus pneumoniae*	0.06	2	3	None; Presumed Persistance	
3495	551	*Streptococcus pneumoniae*	0.12	3	5	*Streptococcus pneumoniae*	0.12
4131	3120	*Streptococcus pneumoniae*	0.06	3	5	*Streptococcus pneumoniae*	0.12
5094	3202	*Streptococcus pneumoniae* *Staphylococcus epidermidis*	0.06 16	3	4	*Staphylococcus epidermidis* *Propionibacterium acnes*	32 0.094
5412	1807	*Streptococcus pneumoniae* *Propionibacterium acnes* *Staphylococcus capitis*	0.12 0.125 0.12	2	2	None; Presumed Persistance	
5488	6101	*Streptococcus pneumoniae* *Propionibacterium acnes*	0.12 0.094	4	5	*Staphylococcus epidermidis* *Propionibacterium acnes*	0.06 0.125
5494	7438	*Streptococcus pneumoniae* *Moraxella catarrhalis*	0.12 0.03	3	5	*Streptococcus pneumoniae*	0.12
3346	8704	*Haemophilus influenzae*	0.03	3	4	*Haemophilus influenzae* *Staphylococcus epidermidis*	≤0.004 1
3568	9232	*Haemophilus influenzae* *Propionibacterium acnes* *Staphylococcus epidermidis*	0.03 0.125 0.06	3	4	*Propionibacterium acnes* *Staphylococcus capitis*	0.125 0.06
4663	4325	*Haemophilus influenzae*	0.015	3	5	*Haemophilus influenzae*	0.015
2449	4611	*Propionibacterium acnes*	0.094	2	3	None; Presumed Persistance	
3631	140	*Propionibacterium acnes* *Staphylococcus epidermidis* *Acinetobacter* species	0.064 0.06 0.25	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.064 0.06
3851	5503	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.19 0.12	3	4	*Propionibacterium acnes*	0.094
4824	7702	*Staphylococcus epidermidis* *Streptococcus mitis*	0.12 0.25	2	2	*Corynebacterium propinquum* *Propionibacterium acnes*	0.12 0.094
5095	4822	*Staphylococcus epidermidis*	0.06	3	4	*Staphylococcus epidermidis*	0.06
5397	2903	*Staphylococcus epidermidis* *Staphylococcus epidermidis*	0.03 0.06	3	3	*Propionibacterium acnes*	0.094
5399	432	*Staphylococcus epidermidis*	0.06	3	4	*Staphylococcus epidermidis*	1
5483	5708	*Staphylococcus epidermidis*	0.12	3	5	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.06
5493	6624	*Staphylococcus epidermidis* *Staphylococcus epidermidis*	1 0.015	3	4	*Staphylococcus epidermidis*	≤0.004
3349	210	*Staphylococcus capitis*	0.06	3	4	*Propionibacterium acnes* *Staphylococcus capitis*	0.125 0.12
4565	8801	*Staphylococcus capitis*	0.12	3	4	*Staphylococcus capitis* *Staphylococcus capitis*	0.12 0.12
5397	2913	*Proteus vulgaris*	1	3	5	*Proteus vulgaris*	2

Source: This submission; TDOC-0011285, Table 4.7.1.-1

Table 31: Microbiological Failures Due to Superinfection – Moxifloxacin AF Treatment Group (MPP)

Inv	Pt	Organisms Isolated at Pre-therapy	MOX[a] MIC (µg/mL)	Days On Therapy	Failure[b] Day	Organisms Isolated at Time of Failure	MOX[a] MIC (µg/mL)
3631	109	*Staphylococcus aureus* *Bacillus pumilus* *Serratia marcescens*	0.06 0.06 2	3	4	*Staphylococcus epidermidis*	16
3631	130	*Staphylococcus aureus* *Propionibacterium acnes* *Staphylococcus epidermidis*	8 0.125 32	3	5	*Staphylococcus epidermidis*	32
3631	135	*Staphylococcus aureus* *Streptococcus oralis*	0.015 0.25	3	4	*Propionibacterium acnes*	0.094
3631	144	*Staphylococcus aureus* *Enterococcus faecalis*	0.03	3	5	*Staphylococcus epidermidis*	16
5418	2805	*Staphylococcus aureus*	0.06	3	4	*Staphylococcus hominis*	0.06
5483	5709	*Staphylococcus aureus*	0.03	3	4	*Staphylococcus capitis*	4
5418	608	*Staphylococcus aureus* *Staphylococcus saprophyticus*	0.06 0.06	3	4	*Streptococcus mitis*	0.12
1913	6705	*Streptococcus pneumoniae*	0.12	3	4	*Streptococcus pneumoniae*	0.06
4131	3110	*Streptococcus pneumoniae* *Propionibacterium acnes*	0.12 0.125	3	4	*Propionibacterium acnes*	0.125
4131	3124	*Streptococcus pneumoniae* *Staphylococcus epidermidis*	0.06 0.06	3	5	*Streptococcus pneumoniae*	0.06
4131	3126	*Streptococcus pneumoniae*	0.06	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.064 0.06
4663	4311	*Haemophilus influenzae* *Propionibacterium* species	0.015 0.094	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.064 0.06
4663	4315	*Haemophilus influenzae* *Propionibacterium acnes* *Staphylococcus epidermidis*	0.015 0.094 0.12	3	4	*Propionibacterium acnes* *Staphylococcus capitis* *Staphylococcus epidermidis*	0.064 0.12 0.06
5096	2103	*Haemophilus influenzae*	0.015	3	4	*Staphylococcus hominis*	0.06
5315	5012	*Haemophilus influenzae* *Bacillus cereus* *Propionibacterium acnes* *Staphylococcus epidermidis*	0.03 0.06 0.064 0.06	3	4	*Bacillus thuringiensis*	0.12
5493	6605	*Haemophilus influenzae* *Streptococcus mitis*	0.015 0.25	3	4	*Actinomyces* species *Propionibacterium acnes* *Staphylococcus capitis*	0.25 0.125 0.12
3631	124	*Propionibacterium acnes* *Staphylococcus capitis*	0.094 0.12	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.06
3631	131	*Propionibacterium acnes*	0.094	3	4	*Dolosigranulum pigrum*	0.015
3851	5513	*Propionibacterium acnes*	0.064	3	4	*Propionibacterium* species *Staphylococcus epidermidis*	0.125 0.06
3920	327	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.06	3	4	*Staphylococcus epidermidis*	0.06
4131	3133	*Propionibacterium acnes* *Staphylococcus capitis*	0.125 0.06	3	4	*Actinomyces* species	0.38
4663	4303	*Propionibacterium acnes*	0.094	3	4	*Staphylococcus epidermidis*	0.06
4663	4313	*Propionibacterium acnes*	0.094	3	5	*Haemophilus influenzae* *Propionibacterium acnes* *Staphylococcus epidermidis*	0.03 0.094 0.12
4811	9425	*Propionibacterium acnes*	0.125	3	5	*Staphylococcus capitis*	0.12

Table 31: Microbiological Failures Due to Superinfection – Moxifloxacin AF Treatment Group (MPP) (continued)

Inv	Pt	Organisms Isolated at Pre-therapy	MOX[a] MIC (µg/mL)	Days On Therapy	Failure[b] Day	Organisms Isolated at Time of Failure	MOX[a] MIC (µg/mL)
4824	7711	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.125 0.06	3	4	*Enterobacter hormaechei* *Leclercia adecarboxylata*	0.06 0.03
5145	9502	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.125 0.06	3	4	*Propionibacterium acnes*	0.125
5264	5216	*Propionibacterium acnes*	0.125	3	4	*Staphylococcus capitis*	0.12
5396	1112	*Propionibacterium acnes*	0.125	3	4	*Propionibacterium acnes*	0.125
5396	1125	*Propionibacterium acnes*	0.094	3	5	*Propionibacterium acnes* *Staphylococcus capitis*	0.094 0.12
5396	1130	*Propionibacterium acnes*	0.064	3	4	*Propionibacterium acnes*	0.047
5399	422	*Propionibacterium acnes*	0.125	3	4	*Propionibacterium acnes*	0.094
5418	604	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.125 0.03	3	4	*Propionibacterium acnes*	0.094
5486	5806	*Propionibacterium acnes*	0.125	3	4	*Staphylococcus epidermidis*	0.015
5489	6209	*Propionibacterium acnes* *Staphylococcus capitis*	0.094 0.06	3	4	*Staphylococcus epidermidis* *Staphylococcus epidermidis*	0.06 0.06
5489	6215	*Propionibacterium acnes*	0.094	3	4	*Escherichia coli*	0.12
5495	7906	*Propionibacterium acnes*	0.094	3	4	*Propionibacterium acnes* *Staphylococcus aureus*	0.125 0.03
5496	6301	*Propionibacterium acnes*	0.064	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.06
3851	5506	*Staphylococcus epidermidis*	0.06	3	5	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.06
4824	7705	*Staphylococcus epidermidis*	1	3	4	*Propionibacterium acnes*	0.094
5095	4806	*Staphylococcus epidermidis*	0.06	3	4	*Enterococcus faecalis*	0.25
5096	2120	*Staphylococcus epidermidis*	0.12	3	4	*Staphylococcus epidermidis*	0.06
5213	3803	*Staphylococcus epidermidis*	0.06	3	5	*Propionibacterium acnes* *Staphylococcus capitis*	0.094 0.12
5265	9905	*Staphylococcus epidermidis*	0.06	3	4	*Propionibacterium acnes*	0.125
5396	1127	*Staphylococcus epidermidis* *Corynebacterium macginleyi*	0.12 0.015	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.125 0.06
5418	605	*Staphylococcus epidermidis*	0.03	3	4	*Staphylococcus hominis*	0.03
5432	3509	*Staphylococcus epidermidis* *Streptococcus mitis* *Streptococcus salivarius*	0.06 0.25 0.06	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.064 0.06
5488	6104	*Staphylococcus epidermidis*	0.03	3	4	*Pseudomonas oryzihabitans* *Pseudomonas plecoglossicida*	2 2
5494	7407	*Staphylococcus epidermidis*	0.06	3	4	*Staphylococcus hominis*	0.06
5532	8401	*Staphylococcus epidermidis*	0.12	3	4	*Propionibacterium acnes* *Staphylococcus capitis*	0.19 0.12
3807	5302	*Staphylococcus capitis*	0.12	3	5	*Propionibacterium acnes*	0.094
5410	1502	*Staphylococcus capitis*	0.12	3	4	*Streptococcus viridans* group	0.12
5412	1812	*Staphylococcus capitis*	0.06	3	5	*Staphylococcus epidermidis*	0.03
5423	1448	*Staphylococcus capitis* *Staphylococcus hominis*	0.12 0.06	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.03
5473	3402	*Staphylococcus capitis* *Corynebacterium propinquum* *Dolosigranulum pigrum*	0.12 0.25 0.03	3	5	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.047 0.06
3568	9236	*Staphylococcus warneri* *Streptococcus mitis*	0.06 0.12	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.06
5526	7512	*Staphylococcus warneri*	0.06	3	5	*Propionibacterium acnes* *Staphylococcus capitis* *Staphylococcus epidermidis*	0.094 0.06 0.06
5409	1304	*Streptococcus* species	0.25	3	5	*Staphylococcus epidermidis*	0.06
4663	4307	*Bacillus* species	0.12	3	4	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.094 0.03
4785	9704	*Bacillus mycoides*	0.03	3	5	*Propionibacterium acnes*	0.094
5495	7911	*Bacillus licheniformis*	0.015	4	5	*Propionibacterium acnes* *Staphylococcus epidermidis*	0.064 0.06
5483	5705	*Rothia mucilaginosa*	0.12	3	4	*Propionibacterium acnes* *Staphylococcus capitis*	0.064 0.06
5494	7432	*Pseudomonas aeruginosa*	2	3	4	*Propionibacterium acnes* *Staphylococcus capitis*	0.094 0.12
3495	554	*Stenotrophomonas maltophilia*	0.06	3	5	*Staphylococcus capitis*	0.12

Source: This submission: TDOC-0011285, Table 4.7.1.-2

There were a small number of fluoroquinolone-resistant isolates recovered in Study C-07-40 (isolates with MIC values greater than the (b) (4) breakpoints for moxifloxacin, ciprofloxacin, and ofloxacin against the species in question). Table 32 summarizes the data for the principle pathogens associated with conjunctivitis. Of note, only 60% (3 of 5) isolates of *Staphylococcus epidermidis* with fluoroquinolone MIC values ≥ 2.0 mcg/ml were eradicated.

Table 32: Antibiotic Susceptibility Profiles of Conjunctivitis Isolates Eradicated (E) or Persisting (P) in Patients Treated with Moxifloxacin AF 0.5% (fluoroquinolone breakpoint = 2 mcg/ml)

Pretherapy Isolates	**E**	**P**
Propionibacterium acnes	1	0
Staphylococcus aureus	2	0
S. capitis	0	0
S. epidermidis	3	2
Streptococcus pneumoniae	0	0
Haemophilus influenzae	0	0

Source: This submission; TDOC-0011285, Table 4.11.-1

STUDY C-04-38

Study C-04-38 was performed in the U.S., with patients enrolled from November 3, 2005 through May 17, 2007. A total of 661 subjects were evaluable in the intent-to-treat (ITT) analyses, 345 in the microbiological intent-to-treat (MBITT) analyses, 342 in the modified intent-to-treat (MITT) analyses, 662 in the per protocol (PP) analyses, and 328 in the modified per protocol (MPP) analyses. Demographics were similar in the two arms, with the majority of subjects between 2 and 11 years of age.

The most frequently isolated bacteria from subjects seen in Study C-04-38 were *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Propionibacterium acnes*, *Staphylococcus epidermidis*, and *S. aureus*. No *Chlamydia trachomatis* was identified in subjects seen in this study. Adenovirus was identified in seven subjects (three in eyes identified as "study eyes").

Microbiological and clinical cure rates at the Day 7 Visit are summarized in Tables 33 and 34, respectively. Early clinical cure (Day 4) rates are summarized in Table 35. In the Moxifloxacin AF treatment group (MPP population), 82.7% (115 of 139) of subjects were identified as microbiological successes, with complete eradication of all pre-therapy pathogens. In the vehicle group, 67.7% (90 of 133) of subjects were classified as microbiological success) Of the clinical failures in this group, 17 of 24 had persisting pathogens. No increased resistance was noted in these isolates (Table 36).

Eradication rates (MPP dataset) for the principle bacterial species associated with bacterial conjunctivitis that were treated in the Moxifloxacin AF group were:

- 89% (25 of 28) *Streptococcus pneumoniae*
- 100% (20 of 20) *Staphylococcus epidermidis*
- 100% (7 of 7) *S. aureus*
- 71% (32 of 45) *Haemophilus influenzae*
- 96% (24 of 25) *Propionibacterium acnes*

Table 33: Microbiological Success Rate at the Day 7 (TOC) Visit

	Treatment								
	Moxi AF				Vehicle				
	Microbiological Outcome				Microbiological Outcome				
	Success		Failure		Success		Failure		
Data Set	N	%	N	%	N	%	N	%	p-value[a]
MBITT	150	84.3	28	15.7	110	65.9	57	34.1	<.0001
MITT	149	84.2	28	15.8	109	66.1	56	33.9	0.0001
MPP	115	82.7	24	17.3	90	67.7	43	32.3	0.0039

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
Source: Table 2.7.3.2.-4; this submission

Table 34: Clinical Cure at the Day 7 (TOC) Visit

	Treatment								
	Moxi AF				Vehicle				
	Clinical Cure at TOC				Clinical Cure at TOC				
	Yes		No		Yes		No		
Data Set	N	%	N	%	N	%	N	%	p-value[a]
ITT	245	74.0	86	26.0	217	65.8	113	34.2	0.0206
MBITT	129	72.5	49	27.5	113	67.7	54	32.3	0.3295
MITT	128	72.3	49	27.7	111	67.3	54	32.7	0.3097
PP	199	75.4	65	24.6	170	65.9	88	34.1	0.0173
MPP	105	75.0	35	25.0	88	66.2	45	33.8	0.1089

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
Source: Table 2.7.3.2.-5; this submission

Table 35: Clinical Cure Rate at the Day 4 (EOT) Visit

	Treatment								
	Moxi AF				Vehicle				
	Clinical Cure				Clinical Cure				
	Yes		No		Yes		No		
Data Set	N	%	N	%	N	%	N	%	p-value[a]
ITT	196	59.2	135	40.8	142	43.0	188	57.0	<.0001
MBITT	104	58.4	74	41.6	78	46.7	89	53.3	0.0293
MITT	103	58.2	74	41.8	77	46.7	88	53.3	0.0329
PP	146	59.1	101	40.9	99	41.9	137	58.1	0.0002
MPP	80	60.6	52	39.4	54	44.3	68	55.7	0.0091

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
Source: Table 2.7.3.2.-5; this submission

Table 36: Moxifloxacin AF Treatment Failures Due to Persistence (MPP – Moxifloxacin AF)

Inv	Pt	Organisms Isolated at Pre-therapy	MOX[a] MIC	Days On Therapy	Failure[b] Day	Organisms Isolated at Time of Failure	MOX[a] MIC
2475	1401	*Haemophilus influenzae*	0.015	3	6	*Haemophilus influenzae*	0.015
		Propionibacterium acnes	0.19				
		Staphylococcus aureus	0.03				
2475	1424	*Haemophilus* species	0.03	3	6	*Haemophilus* species	0.03
2833	202	*Haemophilus influenzae*	0.03	3	6	*Haemophilus influenzae*	0.03
		Moraxella catarrhalis	0.03				
2833	204	*Haemophilus influenzae*	0.06	3	7	*Haemophilus influenzae*	0.06
2833	222	*Haemophilus influenzae*	0.015	3	7	*Haemophilus influenzae*	0.03
		Staphylococcus epidermidis	0.12				
2833	226	*Haemophilus influenzae*	0.008	3	6	*Haemophilus influenzae*	0.008
3475	803	*Haemophilus influenzae*	0.015	3	7	*Haemophilus influenzae*	0.015
		Haemophilus influenzae	0.03			*Streptococcus sanguis*	0.12
		Staphylococcus epidermidis	0.06			*Streptococcus* species	0.12
		Streptococcus pneumoniae	0.12				
3545	303	*Streptococcus pneumoniae*	0.12	3	6	*Streptococcus pneumoniae*	0.12
3545	319	*Haemophilus influenzae*	0.015	3	6	*Haemophilus influenzae*	0.03
		Chryseobacterium indologenes	0.06				
		Streptococcus species	0.06				
4042	1614	*Propionibacterium acnes*	0.094	3	6	*Propionibacterium acnes*	0.19
4055	2307	*Haemophilus influenzae*	0.015	3	8	*Haemophilus influenzae*	0.015
4576	2210	*Streptococcus pneumoniae*	0.015	3	6	*Streptococcus pneumoniae*	0.015
4576	2216	*Haemophilus influenzae*	0.015	3	6	*Haemophilus influenzae*	0.015
4576	2218	*Haemophilus influenzae*	0.03	3	5	*Haemophilus influenzae*	0.03
4580	719	*Haemophilus influenzae*	0.03	3	7	*Haemophilus influenzae*	0.015
		Streptococcus mitis	0.12			*Rothia dentocariosa*	0.12
						Streptococcus pneumoniae	0.12
4795	3018	*Haemophilus influenzae*	0.032	3	7	No specimen collected	
		Streptococcus pneumoniae	0.12				
5006	4001	*Haemophilus influenzae*	0.03	3	7	*Haemophilus influenzae*	0.015

Inv = Investigator
Pt = Patient
[a]Moxifloxacin MIC
[b]Treatment failure day is the day this micro failure occurred on (exam date - baseline date + 1).
Patients could have multiple organisms at pre-therapy and/or exit.

STUDY C-04-40

Study C-04-40 was performed in India, with patients enrolled from May 2, 2006 through December 26, 2006. A total of 695 subjects were evaluable in the intent-to-treat (ITT) analyses, 382 in the microbiological intent-to-treat (MBITT) analyses, 378 in the modified intent-to-treat (MITT) analyses, and 246 in the modified per protocol (MPP) analyses. A significant majority of subjects enrolled in Study C-04-40 were 18 years of age or older (96 subjects less than 18 years of age, 599 subjects aged 18 years and older).

The most frequently isolated bacteria from subjects seen in Study C-04-40 were *Staphylococcus epidermidis*, *S. haemolyticus*, *S. aureus*, and *Micrococcus luteus*. Fifteen cases of *Chlamydia trachomatis* infection were included in the MPP dataset (5 in the Moxifloxacin AF arm, 10 in the Vigamox arm). Report TDOC-0008134 (Study C-04-40) states that adenovirus was recovered, but the number of isolates was not provided. No isolates of either *Streptococcus pneumoniae* or *Haemophilus influenzae* were recovered in Study C-04-40.

The microbiological success rate was 92.6% in the Moxifloxacin AF treatment group, and 92.9% in the VIGAMOX treatment group. Microbiological and clinical cure rates at the Day 7 Visit are summarized in Tables 37 and 38, respectively. Early clinical cure (Day 4) rates are summarized

in Table 39. In the Moxifloxacin AF treatment group (MPP population), 92.6% (112 of 121) of subjects were identified as microbiological successes, with complete eradication of all pre-therapy pathogens. In the Vigamox group, 92.0% (115 of 125) of subjects were classified as microbiological success. Of the clinical failures, no subjects were identified with persisting pathogens.

Eradication rates (MPP dataset) for the principle bacteria associated with bacterial conjunctivitis that were treated in the Moxifloxacin AF group were:

- 100% (33 of 33) *Staphylococcus epidermidis*
- 100% (12 of 12) *S. aureus*
- 100% (6 of 6) *S. haemolyticus*
- 100% (3 of 3) *Chlamydia trachomatis*

Table 37: Microbiological Success Rate at the Day 7 (TOC) Visit

	Treatment											
	Moxi AF				VIGAMOX®							
	Microbiological Outcome				Microbiological Outcome							
	Success		Failure		Success		Failure					
Data Set	N	%	N	%	N	%	N	%	p-value[a]	Delta	LCL[b]	UCL[b]
MBITT	165	87.3	24	12.7	173	89.6	20	10.4	0.4746	-2.3	-8.7406	4.0691
MITT	163	87.2	24	12.8	171	89.5	20	10.5	0.4739	-2.3	-8.8312	4.1052
MPP	112	92.6	9	7.4	115	92.0	10	8.0	0.8689	0.6	-6.1072	7.2311

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
[b]95% Conf. Limits for Moxi AF-VIGAMOX®
Source: Table 2.7.3.2.-8; this submission

Table 38: Clinical Cure at the Day 7 (TOC) Visit

	Treatment											
	Moxi AF				VIGAMOX®							
	Clinical Cure				Clinical Cure							
	Yes		No		Yes		No					
Data Set	N	%	N	%	N	%	N	%	p-value[a]	Delta	LCL[b]	UCL[b]
ITT	279	80.6	67	19.4	289	82.8	60	17.2	0.4587	-2.2	-7.9174	3.5730
MBITT	152	80.4	37	19.6	163	84.5	30	15.5	0.3001	-4.1	-11.6571	3.5918
MITT	150	80.2	37	19.8	161	84.3	30	15.7	0.2991	-4.1	-11.7757	3.6171
PP	197	82.1	43	17.9	197	86.0	32	14.0	0.2442	-3.9	-10.5540	2.6682
MPP	103	84.4	19	15.6	108	85.7	18	14.3	0.7759	-1.3	-10.1614	7.5852

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
[b]95% Conf. Limits for Moxi AF-VIGAMOX®
Source: Table 2.7.3.2.-9; this submission

Table 39: Clinical Cure at the Day 4 (EOT) Visit

	Treatment											
	Moxi AF Clinical Cure				VIGAMOX® Clinical Cure							
	Yes		No		Yes		No					
Data Set	N	%	N	%	N	%	N	%	p-value[a]	Delta	LCL[b]	UCL[b]
ITT	199	57.5	147	42.5	214	61.3	135	38.7	0.3072	-3.8	-11.1001	3.4929
MBITT	109	57.7	80	42.3	125	64.8	68	35.2	0.1547	-7.1	-16.8437	2.6539
MITT	108	57.8	79	42.2	123	64.4	68	35.6	0.1852	-6.6	-16.4539	3.1661
PP	136	58.9	95	41.1	145	64.7	79	35.3	0.1987	-5.8	-14.7694	3.0540
MPP	73	62.4	44	37.6	80	65.0	43	35.0	0.6698	-2.6	-14.8154	9.5204

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
[b]95% Conf. Limits for Moxi AF-VIGAMOX®
Source: Table 2.7.3.2.-10; this submission

SUMMARY OF CLINICAL STUDIES

The two original clinical trials differed significantly in both the demographics of the study populations and in the bacteria isolated from the subjects in these groups. Notably, no isolates of either *Haemophilus influenzae* or *Streptococcus pneumoniae* were recovered in Study C-04-40, despite the fact that these species are considered to be among the most common causes of bacterial conjunctivitis [Mandell 2005]. Similarly, no isolates of *Chlamydia trachomatis* were recovered in Study C-04-38 (or Study C-07-40). These anomalies may be partially explained by the disparity in demographic groups represented in the two trials (Study C-04-38 enrolled primarily subjects ≤ 11 years of age, while Study C-04-40 enrolled primarily patients ≥ 18 years of age) and their geographic location (Study C-04-38 was performed in the U.S., Study C-04-40 was performed in India). Study C-07-40 (this submission) was performed in the U.S. and was similar, demographically, to Study C-04-38, with the exception of the age of enrolled patients (the mean age of patients enrolled in Study C-07-40 was 25.3 years, while the mean age of patients enrolled in Study C-04-38 was 16.8 years (Table 40).

Table 40: Age by Protocol

	Mean	Std	Median	25th Percentile	75th Percentile	N	Min	Max
C-04-38[a]	16.8	17.9	10.0	3.0	27.0	661	0	89
C-04-40[b,c]	37.2	19.4	35.0	22.0	54.0	695	0	87
C-07-40[d]	25.3	23.1	17.0	6.0	42.0	1180	0	92
Total	26.3	22.2	21.0	6.0	42.5	2536	0	92

[a] The youngest patient enrolled was 39 days old.
[b] The youngest patient enrolled was 30 days old.
[c] All patients were from India.
[d] The youngest patient enrolled was 30 days old.
Source: This submission; Table 2.5.4.1.-2

Ocular signs were similar between trials and between arms of each individual study. Most patients had mild to moderate conjunctivitis (Table 41), with severe conjunctival discharge observed more frequently in Study C-04-40.

Table 41: ITT-Baseline Cardinal Ocular Signs

		Moxi AF		VIGAMOX		Vehicle	
		N	%	N	%	N	%
C-07-40	**Bulbar Conjunctival Injection**						
	Normal	0	0.0	0	0.0	0	0.0
	Mild	165	27.8	0	0.0	157	26.8
	Moderate	372	62.7	0	0.0	394	67.2
	Severe	56	9.4	0	0.0	35	6.0
	Conjunctival Discharge/Exudate						
	Absent	2	0.3	0	0.0	1	0.2
	Mild	309	52.1	0	0.0	314	53.6
	Moderate	246	41.5	0	0.0	241	41.1
	Severe	36	6.1	0	0.0	30	5.1
C-04-38	**Bulbar Conjunctival Injection**						
	Normal	2	0.6	0	0.0	0	0.0
	Mild	92	27.9	0	0.0	95	28.8
	Moderate	207	62.7	0	0.0	193	58.5
	Severe	29	8.8	0	0.0	42	12.7
	Conjunctival Discharge/Exudate						
	Absent	0	0.0	0	0.0	2	0.6
	Mild	148	44.8	0	0.0	148	44.8
	Moderate	165	50.0	0	0.0	154	46.7
	Severe	17	5.2	0	0.0	26	7.9
C-04-40	**Bulbar Conjunctival Injection**						
	Normal	0	0.0	0	0.0	0	0.0
	Mild	65	18.8	63	18.1	0	0.0
	Moderate	201	58.1	204	58.5	0	0.0
	Severe	80	23.1	82	23.5	0	0.0
	Conjunctival Discharge/Exudate						
	Absent	1	0.3	1	0.3	0	0.0
	Mild	149	43.1	146	41.8	0	0.0
	Moderate	159	46.0	163	46.7	0	0.0
	Severe	37	10.7	39	11.2	0	0.0

Source: This submission; Table 2.5.4.1.-3

Clinical cure rates for the three Phase 3 studies are summarized in Table 42. Combined results (clinical cure at Day 4) for the two vehicle-controlled studies are summarized in Table 43.

Table 42: Comparison of C-07-40, C-04-38, and C-04-40 Clinical Cure Rates at Day 4 (EOT)

	Clinical Cure Rates (%) by Study		
Treatment Group	**C-07-40[a]**	**C-04-38[a,c]**	**C-04-40[b,c]**
Moxi AF	62.5	58.4	62.4
Vehicle	50.6	46.7	-
VIGAMOX	-	-	65.0
p-value[d]	0.0005	0.0293	0.6698

[a] MBITT data set; superiority studies
[b] MPP data set; noninferiority study
[c] Day 4 sustained cures (patients were cured at Day 4 Visit and remained cured at the subsequent visits)
[d] Chi-square test of independence

Source: Table 2.7.4.3.-1; this submission

Table 43: Clinical Cure at the Day 4 (EOT) Visit (C-07-40 and C-04-38 Combined)

	Treatment											
	Moxi AF Clinical Cure				Vehicle Clinical Cure							
	No		Yes		No		Yes					
Dataset	N	%	N	%	N	%	N	%	Delta	Lower[a]	Upper[a]	p-Value[b]
ITT	356	38.5	568	61.5	464	50.7	452	49.3	12.1	7.6	16.6	<0.0001
MITT	228	38.5	364	61.5	295	50.9	284	49.1	12.4	6.8	18.1	<0.0001
MBITT	233	38.7	369	61.3	298	50.5	292	49.5	11.8	6.2	17.4	<0.0001
PP	298	35.9	488	58.7	381	47.6	384	47.9	11.9	7.0	16.8	<0.0001
MPP	192	35.4	323	59.6	254	48.8	248	47.6	13.3	7.3	19.4	<0.0001

[a] 95% Confidence Limits for Moxi AF - Vehicle
[b] Test = Chi-square (Fishers Exact test if N < 5)

Source: Table 2.5.4.3.-1; this submission

The microbiological success rates for the three clinical trials are summarized in Table 44.

Table 44: Microbiological Success Rates

	Microbiological Success Rates (%)		
Treatment	C-07-40[a]	C-04-38[b]	C-04-40[c]
Moxi AF	74.5	84.3	92.6
Vehicle	56.0	65.9	-
VIGAMOX	-	-	92.0
p-value[d]	<0.0001	<0.0001	0.8689

[a] Day 4 (EOT)/Exit Visit, MBITT
[b] Day 7 (TOC)/Exit Visit, MBITT
[c] Day 7 (TOC)/Exit Visit, MPP
[d] Chi-square test of independence

Source: Table 2.5.4.3.-3; this submission

Data from three Phase 3 clinical trials submitted in support of the Application suggest that Moxifloxacin AF Ophthalmic Solution, 0.5% is effective in eradicating the principle pathogens associated with bacterial conjunctivitis. Eradication rates for all principle pathogens commonly associated with bacterial conjunctivitis were approximately 90% or higher. In cases where *Staphylococcus epidermidis* was isolated (an organism with potential non-susceptibility to fourth-generation fluoroquinolones), 92.9% of the pathogens were eradicated. Increased resistance to moxifloxacin was not noted in isolates defined as persistent pathogens in Study C-07-40 or Study C -04-38 (no persistent pathogens were identified in Study C-04-40). Eradication rates, per pathogen, are presented in Tables 45.

Table 45: Eradication Rates for Conjunctivitis Isolates in Patients Treated with Moxifloxacin AF Ophthalmic Solution (MBITT, Exit Visit) (C-04-38, C-04-40, C-07-40) (species included in proposed package insert of Moxifloxacin AF)

Bacteria Name	Total (N)	Eradicated/ Clinical Cure (N)	Persisted/ Clinical Failure (N)	Eradication Rate (%)
Aerococcus viridans	6	5	1	83.3
Bacillus species[1]	20	19	1	95.0
Corynebacterium macginleyi	7	7	0	100.0
(other) *Corynebacterium* species [2]	10	10	0	100.0
Enterococcus faecalis	6	6	0	100.0
Micrococcus luteus	6	6	0	100.0
Staphylococcus arlettae	8	8	0	100.0
Staphylococcus aureus	38	36	2	100.0
Staphylococcus capitis [3]	25	24	1	96.0
Staphylococcus epidermidis	156	145	11	92.9
Staphylococcus haemolyticus	13	10	3	76.9
Staphylococcus hominis [4]	10	10	0	100.0
Staphylococcus saprophyticus	6	6	0	100.0
Staphylococcus warneri	10	8	2	80.0
other coagulase-negative *Staphylococcus* spp. [5]	15	14	1	93.3
Streptococcus mitis	11	9	2	81.8
Streptococcus pneumoniae	43	39	4	90.7
Streptococcus parasanguinis	5	5	0	100.0
other *Streptococcus* species [6]	20	20	0	100.0
Enterobacter species [7]	5	5	0	100.0
Escherichia coli	6	5	1	83.3
Haemophilus influenzae	109	100	9	91.7
Serratia species [8]	5	5	0	100.0
Propionibacterium acnes	152	139	13	91.4
Chlamydia trachomatis	5	5	0	100.0

Source: adapted from Table 2.7.3.3.2.2.-7, this submission

[1] "*Bacillus* species" includes organisms identified as *Bacillus* sp (3), *B. cereus* (3), *B. circulans* (1), *B. pumilus* (5), *B. simplex* (1), *B. sphaericus* (1), *B. subtilis* (4), and *B. thuringiensis* (2); eradication rate 100% for all except *B. pumilus* (eradication rate = 80%)
[2] "*Corynebacterium* species" includes organisms identified as *Corynebacterium* sp (3), *C. accolens* (2), *C. argentoratense* (1), *C. propinquum* (3), and *C. pseudodiphtheriticum* (1)
[3] "*Staphylococcus capitis*" includes organisms identified as *Staphylococcus capitis* (22) and *S. capitis* subspecies *capitis* (3)
[4] "*Staphylococcus hominis*" includes organisms identified as Staphylococcus hominis (6) and *S. hominis* subspecies *novobiosepticus* (4)
[5] "other coagulase-negative *Staphylococcus* species" includes organisms identified as *S. caprae* (3), *S. cohnii* (4), *S. gallinarum* (1), *S. lentus* (1), *S. pasteuri* (2), and *S. sciuri* (4); eradication rate 100% for all except *S. cohnii* (eradication rate = 75.0%)
[6] "other *Streptococcus* species" includes organisms identified as *Streptococcus* species (9), *S. cristatus* (1), *S. gordonii* (1), *S. oralis* (1), *S. peroris* (2), *S. sanguis* (1), *S. thermophilus* (1), and *Streptococcus viridans* group (4)
[7] "*Enterobacter* species" includes organisms identified as *Enterobacter cloacae* (2), and *E. hormaechei* (3)
[8] "*Serratia* species" includes organisms identified as *Serratia* species (1), *S. liquefaciens* (1), and *S. marcescens* (3)

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Kerry Snow MS
Microbiology Reviewer
14 July 2010

Fred Marsik, Ph.D.
MicroTL/HFD-520
24 Aug 10 FIN FJM

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22428	ORIG-1	ALCON PHARMACEUTICALS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

KERRY SNOW
08/24/2010

FREDERIC J MARSIK
08/24/2010

Product Quality Microbiology Review

28 SEPTEMBER 2009

NDA: 22-428/N-000

Drug Product Name

Proprietary: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution

Non-proprietary: moxifloxacin hydrochloride ophthalmic solution 0.5% as base

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
12 December 2008	15 December 2008	12 January 2009	13 January 2009
10 February 2009	11 February 2009	n/a	18 February 2009

Submission History (for amendments only): N/A

Applicant/Sponsor

Name: Alcon Pharmaceuticals Ltd.

Address: Route des Arsenaux 41
1700 Fribourg
Switzerland

Representative: Karen S. Lankow
Assoc. Dir. Regulatory Affairs
Alcon Research Ltd.
6201 South Freeway
Fort Worth, TX 76134-2099
(Authorized U.S. Agent)

Telephone: 817-568-6494

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint. Two Comments are provided for the Applicant (see Review Section 3).

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA 505(b)(1)

2. SUBMISSION PROVIDES FOR: Marketing Authorization

3. MANUFACTURING SITE:
Drug Product Manufacturing and Testing Facility:
Alcon Research, Ltd.
ASPEX Manufacturing facility
6201 south Freeway
Fort Worth, TX 76134

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile solution; topical ocular; 0.5% as base (0.545% w/v), (b) (4) and 3ml fill volumes in 4ml DROP-TAINER plastic containers.

5. METHOD(S) OF STERILIZATION: (b) (4) Processing subsequent to: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Antibacterial agent

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Review #1 for NDA 21-598/SCM-013 (for VIGAMOX), report dated 13 December 2006 (DARRTS date 14 December 2006).
- Microbiology Review #1 for NDA 21-598/SCM-016 (for VIGAMOX), report dated 02 MAY 2008 (DARRTS date 05 MAY 2008).
- Microbiology Review #1 for (b) (4) (Moxifloxacin HCl Ophthalmic Solution, 0.5%) report dated 12 March 2003 (DARRTS date 21 MARCH 2003).

C. REMARKS:

- The ONDQA Initial Quality Assessment was filed on 18 June 2009. The chemist recommended that microbiology assess the specification for bacterial endotoxin (NLT (b) (4)) and the lack of a routine release assay for (b) (4) effectiveness.
- The submission is a paper technical submission (white binders) in CTD format.

Filename: N022428N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval (with two COMMENTS)

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 (b) (4)

B. Brief Description of Microbiology Deficiencies – No deficiencies. There are two COMMENTS related to the specification and analysis method for bacterial endotoxins. (See Review Section 3).

C. Assessment of Risk Due to Microbiology Deficiencies - The drug product is (b) (4) using properly validated processes. Therefore, the drug product presents a minimal risk from the standpoint of product quality microbiology.

III. Administrative

A. Reviewer's Signature _____
Robert Mello, Ph.D.

B. Endorsement Block_____
Bryan S. Riley, Ph.D.

C. CC Block
NDA 22-428

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22428	ORIG-1	ALCON PHARMACEUTICALS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP
NDA-22428	ORIG-1	ALCON PHARMACEUTICALS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

ROBERT J MELLO
09/29/2009

BRYAN S RILEY
09/29/2009
I concur.

Division of Anti-Infective and Ophthalmology Products
Clinical Microbiology Review

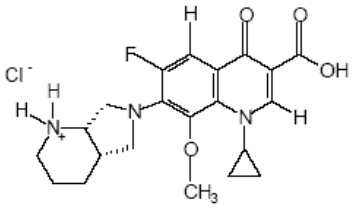
NDA: 022428
Date Company Submitted: 15 December 2008
Date Assigned: 8 January 2009
Date Completed: 30 June 2009
Reviewer: Kerry Snow MS

NAME AND ADDRESS OF APPLICANT:
Alcon Pharmaceuticals Ltd.
Route des Arsenaux 41
1700 Fribourg
Switzerland

CONTACT PERSON:
US Agent:
Alcon Research Ltd.
Mail Code R3-52
6201 South Freeway
Fort Worth, TX 76134-2099
Karen Lankow, Assoc. Director, Regulatory Affairs
817-568-6494

DRUG PRODUCT NAMES:
Proprietary Name: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution
Proposed Trade Name: Moxifloxacin AF
Code Names: AL-15469A (Alcon); BAY 12-8039 (Bayer)
Established Name: Moxifloxacin hydrochloride ophthalmic solution 0.5% as base (equivalent to 5 mg moxifloxacin per mL)
Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolol[3,4-*b*]pyridine-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

STRUCTURAL FORMULA:



MOLECULAR FORMULA:
$C_{21}H_{24}FN_3O_4 \cdot HCl$

MOLECULAR WEIGHT:
437.9

DRUG CATEGORY:
Antimicrobial

PROPOSED DOSAGE FORM AND STRENGTH:

Sterile ophthalmic solution of moxifloxacin hydrochloride, 0.5% as base
3 mL in a 4 mL bottle

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:
Instill 1 drop in the affected eye(s) 2 times daily for 7 days

DISPENSED:
Rx

PROPOSED INDICATION:
Treatment of bacterial conjunctivitis

RELATED DOCUMENTS:
NDA 021085 Avelox (original approval 10 December 1999)
NDA 021598 Vigamox (original approval 15 April 2003)
(b) (4)

TYPE OF SUBMISSION:
New Drug Application

PURPOSE OF SUBMISSION:

This New Drug Application (NDA) is submitted to seek approval for the use of an alternative formulation of moxifloxacin hydrochloride ophthalmic solution (Moxifloxacin AF) for the treatment of bacterial conjunctivitis in adults and pediatric patients one year or older.

REMARKS:

This review is based on information submitted by the Applicant on December 12, 2008 (NDA 22428), including the Applicants summaries of studies performed to support the NDA, and microbiological data provided by the central testing laboratories, (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) This review does not address methods of moxifloxacin susceptibility testing or quality control parameters that would be employed during those procedures. Breakpoints for antimicrobial susceptibility testing are not required for antimicrobials intended for topical administration, and these have not been proposed in this NDA. Criteria for inclusion of organisms in the proposed label was discussed with the Applicant prior to the submission of this NDA ["organisms that are cultured from an eye with conjunctivitis and treated with moxifloxacin in 5 or more cases with a ≥ 80% eradication rate or cultured from an eye with conjunctivitis and treated with besifloxacin in 10 or more cases with a ≥ 50% eradication rate"]. These criteria have been used in this review to determine the appropriate organisms for inclusion in the INDICATIONS AND USAGE section of the proposed label. The Applicant has provided summary information from recent literature to support inclusion of "second list" microorganisms in the proposed label.

The Applicant has referenced NDA 21-598 for VIGAMOX (Alcon Research, LTD) and NDA 21-085 for moxifloxacin hydrochloride tablets (Bayer Corporation) in support of the Application, and has provided documentation for rights of reference.

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).

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. IN VITRO INFORMATION

MECHANISM OF ACTION

Moxifloxacin, a fourth-generation fluoroquinolone, acts by disrupting two bacterial enzymes, DNA gyrase and DNA topoisomerase IV (both categorized as type 2 topoisomerases).
The Applicant has performed no new studies of the mechanism of action of moxifloxacin. Reference is made to NDA 021598 (Vigamox, approved 15 April 2003).

ANTIMICROBIAL SPECTRUM OF ACTIVITY

In in vitro studies, using systemic interpretation criteria for antimicrobial activity, moxifloxacin has demonstrated activity against bacteria commonly associated with bacterial conjunctivitis, including *Staphylococcus aureus*, *S. epidermidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Propionibacterium acne*, and *Chlamydia trachomatis*. These organisms, as well as others listed in the proposed label, should be susceptible to moxifloxacin at the concentration that is available per drop of solution (0.25 mg/drop). Data from in vitro susceptibility testing of isolates collected during Phase 3 clinical trials supports the inclusion of these and the other bacteria listed in the proposed indications for Moxifloxacin AF Ophthalmic Solution. The Applicant has provided a summary of data describing the in vitro activity of moxifloxacin against bacterial isolates not recovered in sufficient quantities from the two clinical trials. This data, collected from over 300 recent publications, supports the inclusion of these microorganisms in the proposed label's "second list" of bacteria, where in vitro data are available but their clinical significance in ophthalmic infections is unknown, and where the safety and effectiveness of Moxifloxacin AF has not been established. The concentration of moxifloxacin in Moxifloxacin AF Ophthalmic Solution is 5 mg/mL. At the recommended dose (0.50 mg moxifloxacin in 2 drops) initial exposure of the antibiotic is in significant excess, compared to the MIC_{range} of all pathogens listed in the proposed label.

RESISTANCE STUDIES

The Applicant has submitted no new information regarding the mechanisms of resistance to moxifloxacin among isolates commonly associated with bacterial conjunctivitis. Recent studies, including literature surveys compiled by the Applicant, suggest decreased susceptibility to moxifloxacin in certain bacterial species, including *Staphylococcus epidermidis* and some *Corynebacterium* species. No development of resistance to moxifloxacin was noted in the two clinical trials of Moxifloxacin AF Ophthalmic Solution.

II. HUMAN AND ANIMAL STUDIES

ANIMAL DISEASE MODELS

The Applicant has submitted a report (TDOC-00200) from a study designed to investigate the in vivo efficacy of Moxifloxacin AF Ophthalmic Solution, compared to VIGAMOX, levofloxacin, and CILOXAN (only used as a comparator in tests against *Pseudomonas aeruginosa*). The studies suggest that Moxifloxacin AF is more effective in early therapy treatment than VIGAMOX against *S. aureus* isolates susceptible to quinolones, similar to VIGAMOX but more effective than

levofloxacin against *S. aureus* in late stage therapy models. No statistical difference was noted between comparators in treating isolates of quinolone-resistant *S. aureus* in early stage models. Against *Pseudomonas aeruginosa*, all moxifloxacin preparations were similarly effective, and all were less effective than levofloxacin. In prophylaxis models, all moxifloxacin preparations behaved similarly against *S. aureus* infection in both 30-minute and 3-hour pre-infection treatment regimens. Against *P. aeruginosa*, Moxifloxacin AF prophylaxis was more effective than VIGAMOX, but less effective than levofloxacin or CILOXAN.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

In a study designed to investigate the concentration of Moxifloxacin AF in tear film, New Zealand white rabbits were dosed once with Moxifloxacin AF or VIGAMOX. Moxifloxacin AF concentrations exceeded those of VIGAMOX at all sampling times, although the difference decreased over time. $AUC_{0\text{-}16\ min}$ for Moxifloxacin AF was significantly higher than that of VIGAMOX. Similarly, in a study designed to investigate the concentration of Moxifloxacin AF in the aqueous humor of New Zealand white rabbits, following a single administration, Moxifloxacin AF concentration exceeded that of VIGAMOX at each sampling point. $AUC_{0\text{-}120\ min}$ was significantly higher for the Moxifloxacin AF-treated animals than for the VIGAMOX-treated group. Results from Study C-05-15 (a Phase 1 clinical trial, enrolling 30 subjects) indicate rapid absorption of moxifloxacin, with C_{max} (0.977 ng/ml) attained within one hour of dosing. Steady-state concentrations were attained by Day 3 of a twice-daily (every 12 hours) dosing regimen. Systemic exposure over the 12-hour dosing interval ($AUC_{0\text{-}12}$) averaged 8.17 ± 5.31 ng*h/mL.

III. CLINICAL TRIALS

Data from the two Phase 3 clinical trials submitted in support of the Application suggest that Moxifloxacin AF Ophthalmic Solution, 0.5% is effective in eradicating the principle pathogens associated with bacterial conjunctivitis. With the exception of *Haemophilus influenzae* (eradiation rate = 71% in patients treated with Moxifloxacin AF), eradication rates for all principle pathogens commonly associated with bacterial conjunctivitis were approximately 90% or higher. In cases where *Staphylococcus epidermidis* was isolated (an organism with potential non-susceptibility to fourth-generation fluoroquinolones), 100% of the pathogens were eradicated. Increased resistance to moxifloxacin was not noted in isolates defined as persistent pathogens in Study 04-38 (no persistent pathogens were identified in Study C-04-40).

The two clinical trials differed significantly in both the demographics of the study populations and in the bacteria isolated from the subjects in these groups. Notably, no isolates of either *Haemophilus influenzae* or *Streptococcus pneumoniae* were recovered in Study C-04-40, despite the fact that these species are considered to be among the most common causes of bacterial conjunctivitis [Mandell 2005]. Similarly, no isolates of *Chlamydia trachomatis* were recovered in Study C-04-38. These anomalies may be partially explained by the disparity in demographic groups represented in the two trials (Study C-04-38 enrolled primarily subjects ≤ 11 years of age, while Study C-04-40 enrolled primarily patients ≥ 18 years of age) and their geographic location (Study C-04-38 was performed in the U.S., Study C-04-40 was performed in India).

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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_3 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 (Ocuflox), and besifloxacin (Besivance).

Moxifloxacin hydrochloride (Avelox) was approved in 1999 (NDA 21-085) as an oral tablet for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and mild to moderate community-acquired pneumonia, and was later approved for the treatment of uncomplicated skin and skin structure infections. Alcon referenced NDA 21-085 in its application for Vigamox (moxifloxacin hydrochloride solution/drops; ophthalmic, NDA 21-598), which was approved in 2003 for the treatment of bacterial conjunctivitis.

MOXIFLOXACIN ALTERNATIVE FORMULATION (AF) OPHTHALMIC SOLUTION

This application references NDA 21-085 (Avleox) and NDA 21-598 (VIGAMOX). The Applicant is submitting this NDA for an alternative formulation of moxifloxacin hydrochloride ophthalmic solution. Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution is intended to (b) (4) (b) (4) (b) (4) allowing for reduced dosing requirements (reduced from 3 times per day to 2 times per day). A xanthan (b) (4) has been added to the formulation to accomplish these goals. The differences between the original (VIGAMOX) formulation and the Moxifloxacin AF formulation are summarized in Table 1.

Antimicrobial activity and efficacy of Moxifloxacin AF formulation is principally supported, in this Application, by data from two Phase 3 clinical trials, including one active-controlled trial performed in India (Protocol C-04-40) and one vehicle-controlled trail performed in the U.S. (Protocol C-04-38).

Table 1: Comparison of Compositions of Moxifloxacin AF and VIGAMOX

Component	% Composition	
	Moxifloxacin AF	VIGAMOX
Moxifloxacin HCl	0.545	Same
Sodium Chloride	(b) (4)	(b) (4)
Xanthan Gum		
Boric Acid		
Sorbitol		
Tyloxapol		
Sodium Hydroxide and/or Hydrochloric Acid	Adjust to pH 7.4	Adjust to pH 6.8
Purified Water	(b) (4)	(b) (4)

Source: This submission, Table 2.3.P.2-1

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].

No new information has been provided, concerning the mechanism of action of moxifloxacin. This Application references information submitted in NDA 21-598 (Vigamox), concerning studies performed to describe the mechanism of action of moxifloxacin.

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].

The Applicant has submitted no "pre-clinical" in vitro antimicrobial data from studies conducted specifically in support of this Application. Data describing the in vitro activity of moxifloxacin against isolates recovered in the clinical trials conducted to support this NDA are used to support the inclusions of specific microorganisms in the Indications section of the proposed label.

The Applicant has submitted summary information from a literature search designed to describe a current antimicrobial profile for moxifloxacin against bacterial isolates included in the "second list" of microorganisms (guidance to clinicians, where only in vitro data are available) in the proposed label for Moxifloxacin AF Ophthalmic Solution, 0.5%. This information is summarized in Tables 1 through 3. Included in the tables are references to summary data from clinical trials discussed later in this review (reference labeled "Alcon Studies 2005 to 2008") and data from Alcon trials used to support NDA 21-598 (VIGAMOX)(Report TDOC-0000208).

Of the referenced studies compiled by the Applicant in support of this NDA or NDA 21-598 (VIGAMOX), most were conducted outside the U.S. Many of the referenced studies were performed at least 10 years prior to this Application. Some studies (e.g. Bauernfeind et al. 1997) did not reference methods approved by CLSI, and some studies (e.g. FungTomc et al. 2000) did not report quality control procedures. A number of the studies did not investigate a sufficient number of isolates (≥10) to report an MIC_{90} value for a particular species (although several studies reported an MIC_{90} value, nonetheless). Several studies reported non-susceptible values for moxifloxacin against reported pathogens (e.g. Soussy, et al. 2003: moxifloxacin MIC_{90} = 16 mcg/ml against isolates of *Enterococcus faecalis*, n=125).

Table 1: Moxifloxacin Activity Against Aerobic Gram Positive Microorganisms

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Bacillus anthracis (Total Isolates = 18)							
Bacillus anthracis	18	≤ 0.25	≤0.25-≤0.25	Broth dilution	US	Luna VA et al.	2007
Bacillus cereus (Total Isolates = 91							
Bacillus cereus	11	0.12	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Bacillus cereus	38	0.12	0.032 - 0.25	Broth dilution	US	TDOC-0000208	2003
Bacillus cereus	42	≤ 0.25	≤0.25-≤0.25	Broth dilution	US	Luna VA et al.	2007
Bacillus thuringiensis (Total Isolates = 26)							
Bacillus thuringiensis	7	--	0.06 - 0.25	Broth dilution	US	TDOC-0000208	2003
Bacillus thuringiensis	19	≤ 0.25	≤0.25-≤0.25	Broth dilution	US	Luna VA et al.	2007
Corynebacterium accolens (Total Isolates = 11)							
Corynebacterium accolens	11	0.50	0.015 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium macginleyi (Total Isolates = 38)							
Corynebacterium macginleyi	38	0.12	0.004 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium propinquum (Total Isolates = 29)							
Corynebacterium propinquum	29	0.25	0.25 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium pseudodiphtheriticum (Total Isolates = 95)							
Corynebacterium pseudodiphtheriticum	95	0.25	0.12 – 0.50	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium striatum (Total Isolates = 34)							
Corynebacterium striatum	16	0.12	0.06 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Corynebacterium striatum	18	0.047	0.038 - 8.0	E test	Non-US	Sierra JM et al.	2005
Enterococcus faecalis (Total Isolates = 3357)							
Enterococcus faecalis	79	0.50	0.03 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Enterococcus faecalis	18	0.50	0.25 - 8.0	Agar dilution	US & Non-US	FungTome et al.	2000
Enterococcus faecalis	66	1.0	≤0.5 - 4.0	Agar dilution	Non-US	Del Campo R et al.	2003
Enterococcus faecalis	76	≤0.5	≤0.5 - 4.0	Agar dilution	Non-US	Del Campo R et al.	2003
Enterococcus faecalis	125	16	0.12 - 32	Broth dilution	Non-US	Soussy CJ et al.	2003
Enterococcus faecalis	25	8.0	0.25 - 16	Agar dilution	Non-US	Otani T et al.	2003
Enterococcus faecalis	21	0.5	0.19 - 0.5	E test	Non-US	Pineheiro ET et al.	2004
Enterococcus faecalis	100	1.0	0.12 - 1.0	Agar dilution	Non-US	Bauernfeind et al.	1997
Enterococcus faecalis	30	0.50	0.12 - 4.0	Agar dilution	Non-US	Woodcock et al.	1997
Enterococcus faecalis	2804	0.25	0.03 -16	Broth dilution	Non-US	Schouten et al.	1999
Enterococcus faecalis	13	0.50	0.03 - 8.0	Agar dilution	Non-US	Pong et al.	1999
Kocuria kristinae (Total Isolates = 12)							
Kocuria kristinae	6	--	0.12 – 1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Kocuria kristinae	6	--	0.25 - 0.25	Broth dilution	US	TDOC-0000208	2003
Staphylococcus caprae (Total Isolates = 65)							
Staphylococcus caprae	36	0.12	0.03 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus caprae	29	0.12	0.06 - 0.12	Broth dilution	US	TDOC-0000208	2003
Staphylococcus cohnii (Total Isolates = 35)							
Staphylococcus cohnii	6	--	0.12 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus cohnii	8	--	0.06 - 0.50	Broth dilution	US	TDOC-0000208	2003
Staphylococcus lugdunensis (Total Isolates = 80)							
Staphylococcus cohnii	21	0.06	0.03 - 0.50	Agar dilution	Non-US	Bauernfeind et al.	1997
Staphylococcus lugdunensis	33	0.12	0.06 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus lugdunensis	47	0.25	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Staphylococcus pasteuri (Total Isolates = 32)							
Staphylococcus pasteuri	9	--	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus pasteuri	23	0.25	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Staphylococcus saprophyticus (Total Isolates = 63)							
Staphylococcus saprophyticus	6	--	0.12 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Staphylococcus saprophyticus	27	0.25	0.12 - 0.25	Broth dilution	US	TDOC-0000208	2003

Table 1: Moxifloxacin Activity Against Aerobic Gram Positive Microorganisms (cont'd)

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Staphylococcus saprophyticus	30	0.25	0.12 - 0.25	Agar dilution	Non-US	Woodcock et al.	1997
Streptococcus agalactiae (Total Isolates = 167)							
Streptococcus agalactiae	18	0.25	0.12 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus agalactiae	10	0.25	0.25 - 0.25	Agar dilution	US & Non-US	FungTome et al.	2000
Streptococcus agalactiae	30	0.25	0.12 - 0.5	Agar dilution	Non-US	King A et al.	2004
Streptococcus agalactiae	26	0.12	0.03 - 0.12	Broth dilution	Non-US	Hoogkamp-Korstanje & Roelofs-Willemse	2000
Streptococcus agalactiae	20	0.25	0.06 - 0.50	Agar dilution	Non-US	Woodcock et al.	1997
Streptococcus agalactiae	38	0.50	0.06 - 0.50	Agar dilution	Non-US	Bauernfeind et al.	1997
Streptococcus agalactiae	25	0.25	0.12 - 0.50	Broth dilution	Non-US	Barry et al.	1999
Streptococcus milleri group (Total Isolates = 79)							
Streptococcus milleri group	79	0.25	0.06 - 0.5	Broth dilution	Non-US	Yamamoto N et al.	2006
Streptococcus mitis (Total Isolates = 241)							
Streptococcus mitis	92	0.25	0.06 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus mitis	94	0.25	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Streptococcus mitis	10	0.12	0.06 - 0.12	Agar dilution	US	Goldstein et al.	2000
Streptococcus mitis	17	0.50	0.12 - 0.50	Agar dilution	US & Non-US	FungTome et al.	2000
Streptococcus mitis	25	0.25	0.06 - 0.25	Broth dilution	Non-US	Hoogkamp-Korstanje & Roelofs-Willemse	2000
Streptococcus mitis	3	0.5	0.12 - 0.5	Broth dilution	Non-US	Presterl E et al.	2005
Streptococcus oralis (Total Isolates = 25)							
Streptococcus oralis	20	0.25	0.12 – 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus oralis	2	0.12	0.12-0.12	Broth dilution	Non-US	Presterl E et al.	2005
Streptococcus oralis	3	0.25	0.06 - 0.25	Broth dilution	Non-US	Presterl E et al.	2005
Streptococcus parasanguinis (Total = 19)							
Streptococcus parasanguinis	19	0.25	0.12 – 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus pyogenes (Total Isolates = 642)							
Streptococcus pyogenes	52	0.25	0.12 – 0.50	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus pyogenes	419	0.25	<0.03 - 0.5	Agar dilution	Non-US	Hsueh PR et al.	2003
Streptococcus pyogenes	40	0.12	--	Broth dilution	Non-US	Noviello S et al.	2003
Streptococcus pyogenes	25	0.5	0.12 - 0.5	Agar dilution	Non-US	Otani T et al.	2003
Streptococcus pyogenes	66	0.25	0.06 - 0.5	Broth dilution	Non-US	Liebowitz LD et al.	2003
Streptococcus pyogenes	40	0.25	0.06 - 0.5	Agar dilution	Non-US	King A et al.	2004
Streptococcus salivarius (Total Isolates = 46)							
Streptococcus salivarius	25	0.50	0.06 – 8.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus salivarius	21	0.12	0.06 - 0.25	Broth dilution	US	TDOC-0000208	2003
Streptococcus sanguis (Total Isolates = 11)							
Streptococcus sanguis	9	--	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Streptococcus sanguis	2	--	0.06 - 0.25	Broth dilution	Non-US	Presterl E et al.	2005
Acinetobacter baumannii (Total Isolates = 164)							
Acinetobacter baumannii	27	0.25	0.03 - 0.50	Broth dilution	US	TDOC-0000208	2003
Acinetobacter baumannii	7	8.0	0.0625 - 8.0	Broth dilution	US	Jung R et al.	2007
Acinetobacter baumannii	18	1.0	0.06 – 2.0	Agar dilution	US & Non-US	FungTome et al.	2000
Acinetobacter baumannii	41	32	0.032 - 64	Broth dilution	Non-US	Soussy CJ et al.	2003
Acinetobacter baumannii	22	1.0	0.25 - 1.0	E test	Non-US	Spence RP et al.	2003
Acinetobacter baumannii	43	0.25	0.008 – 2.0	Agar dilution	Non-US	Bauernfeind et al.	1997
Acinetobacter baumannii	11	2.0	0.008 - 16	Agar dilution	Non-US	Woodcock et al.	1997
Acinetobacter calcoaceticus (Total Isolates = 66)							
Acinetobacter calcoaceticus	13	0.12	0.03 - 64	Agar dilution	US	Higgins et al.	2000
Acinetobacter calcoaceticus	3	--	0.06 - 0.06	Broth dilution	US	TDOC-0000208	2003
Acinetobacter calcoaceticus	30	0.25	<0.003 – 2.0	Agar dilution	Non-US	Dalhoff et al.	1996
Acinetobacter calcoaceticus	20	0.06	0.008 - 0.06	Agar dilution	Non-US	Bauernfeind	1997
Acinetobacter junii (Total Isolates = 33)							
Acinetobacter junii	33	0.12	0.03 - 8.0	Broth dilution	US	TDOC-0000208	2003
Acinetobacter lwoffi (Total Isolates = 9)							
Acinetobacter lwoffi	9	--	0.032 - 0.5	Broth dilution	Non-US	Soussy CJ et al.	2003

Table 1: Moxifloxacin Activity Against Aerobic Gram Positive Microorganisms (cont'd)

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Acinetobacter schindleri (Total Isolates = 26)							
Acinetobacter schindleri	26	0.06	0.016 - 0.06	Broth dilution	US	TDOC-0000208	2003
Acinetobacter ursingii (Total Isolates = 13)							
Acinetobacter ursingii	13	0.50	0.06 - 1.0	Broth dilution	US	TDOC-0000208	2003
Aeromonas spp. (Total Isolates = 57)							
Aeromonas caviae	9	--	0.03 - 8.0	Broth dilution	US	TDOC-0000208	2003
Aeromonas hydrophila	16	0.12	0.06 - 0.12	Agar dilution	US & Non-US	FungTomc et al.	2000
Aeromonas hydrophila	32	0.03	0.008 - 0.06	Agar dilution	Non-US	Bauernfeind et al.	1997
Chryseobacterium indologenes (Total Isolates = 13)							
Chryseobacterium indologenes	4	--	0303 – 0.06	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Chryseobacterium indologenes	9	--	0.03 - 2.0	Broth dilution	US	TDOC-0000208	2003
Enterobacter aerogenes (Total Isolates = 13)							
Enterobacter aerogenes	7	0.25	0.06 – 0.12	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Enterobacter aerogenes	17	0.25	0.03 - 1.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Enterobacter aerogenes	11	0.50	0.12 - 0.50	Broth dilution	US	TDOC-0000208	2003
Enterobacter aerogenes	42	2.0	0.03 - 4.0	Agar dilution	Non-US	Bauernfeind	1997
Enterobacter cloacae (Total Isolates = 108)							
Enterobacter cloacae	27	0.12	0.06-0.50	Broth Dilution	US	Alcon Studies 2005 to 2008	2005 2008
Enterobacter cloacae	63	0.06	0.016 -16	Agar dilution	Non-US	Bauernfeind	1997
Enterobacter cloacae	18	0.25	0.06 - 0.50	Agar dilution	US & Non-US	FungTomc et al.	2000
Haemophilus parainfluenzae (Total Isolates = 34)							
Haemophilus parainfluenzae	23	0.12	0.015 -0.25	Broth dilution	US	Bogdanovich T et al.	2006
Haemophilus parainfluenzae	11	0.12	0.008-0.25	Agar dilution	Non-US	Soussy CJ et al.	2003
Klebsiella oxytoca (Total Isolates = 1668)							
Klebsiella oxytoca	12	0.25	0.06 – 0.25	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Klebsiella oxytoca	44	1.0	0.03 - 16	Agar dilution	Non-US	Soussy CJ et al.	2003
Klebsiella oxytoca	1612	2.0	--	Broth dilution	US & Non-US	Sader HS et al.	2007
Klebsiella oxytoca	1	--	1.0 - 1.0	Agar dilution	Non-US	Lascols C et al.	2007
Moraxella catarrhalis (Total Isolates = 8780)							
Moraxella catarrhalis	127	0.06	0.015 – 0.50	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Moraxella catarrhalis	218	0.06	--	Broth dilution	US	Jacobs MR et al.	2004
Moraxella catarrhalis	5981	0.06	--	Broth dilution	US & Non-US	Jones RN et al.	2007
Moraxella catarrhalis	1656	0.06	--	Broth dilution	US & Non-US	Jones RN et al.	2003
Moraxella catarrhalis	256	0.06	≤0.002 - 0.25	Broth dilution	Non-US	Liebowitz LD et al.	2003
Moraxella catarrhalis	30	0.12	--	Broth dilution	Non-US	Noviello S et al.	2003
Moraxella catarrhalis	85	0.06	≤0.004 - 0.25	Agar dilution	Non-US	Kucukbasmaci et al.	2003
Moraxella catarrhalis	40	0.25	0.016 - 0.25	Agar dilution	Non-US	Soussy CJ et al.	2003
Moraxella catarrhalis	25	0.06	0.03 - 0.12	Agar dilution	Non-US	Otani T et al.	2003
Moraxella catarrhalis	29	0.03	0.015-0.06	Broth dilution	Non-US	Bowker KE et al.	2003
Moraxella catarrhalis	5	0.06	0.062 - 0.062	Broth dilution	Non-US	Drago L et al.	2004
Moraxella catarrhalis	269	0.06	0.03 - 1.0	Agar dilution	Non-US	Morrissey I et al.	2005
Moraxella catarrhalis	46	0.25	0.06 - 8.0	Agar dilution	Non-US	Ling TKW et al.	2005
Moraxella catarrhalis	9	--	0.06 - 0.12	Broth dilution	Non-US	Bogdanovich et al.	2006
Moraxella catarrhalis	40	0.12	≤0.06 - 0.25	Broth dilution	Non-US	Bogdanovich et al.	2006
Moraxella osloensis (Total Isolates = 20)							
Moraxella osloensis	20	0.25	0.03 - 0.25	Broth dilution	US	TDOC-0000208	2003

Table 1: Moxifloxacin Activity Against Aerobic Gram Positive Microorganisms (cont'd)

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Morganella morganii (Total Isolates = 121)							
Morganella morganii	18	0.50	0.12 - 0.50	Agar dilution	US & Non-US	FungTomc et al.	2000
Morganella morganii	41	0.12	0.03 - 8.0	Agar dilution	Non-US	Bauernfeind	1997
Morganella morganii	15	0.25	0.03 - 0.25	Agar dilution	Non-US	Woodcock et al.	1997
Morganella morganii	47	16	0.063 - 128	Agar dilution	Non-US	Soussy CJ et al.	2003
Neisseria gonorrhoeae (Total Isolates = 240)							
Neisseria gonorrhoeae	34	0.015	0.004 - 0.012	Agar dilution	Non-US	Woodcock et al.	1997
Neisseria gonorrhoeae	31	0.06	0.002 - 0.12	Agar dilution	Non-US	Ruiz J et al.	2003
Neisseria gonorrhoeae, ampicillin^{R}	14	0.03	0.016 - 0.06	Agar dilution	Non-US	Bauernfeind	1997
Neisseria gonorrhoeae, ampicillin^{S}	20	0.016	0.002 - 0.016	Agar dilution	Non-US	Bauernfeind	1997
Neisseria gonorrhoeae, ofloxacin^{S}	23	0.25	≤0.004 - 0.25	Agar dilution	Non-US	Otani T et al.	2003
Neisseria gonorrhoeae, ciprofloxacin^{S}	35	0.03	0.004 - 0.06	Agar dilution	US & Non-US	FungTomc et al.	2000
Neisseria gonorrhoeae, quinolone^{R}	50	0.50	0.06 - 2.0	Agar dilution	US & Non-US	Jones et al.	2000
Neisseria gonorrhoeae, ciprofloxacin^{R}	10	1.0	0.12 - 1.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Neisseria gonorrhoeae, ofloxacin^{R}	23	8.0	1.0 - 8.0	Agar dilution	Non-US	Otani T et al.	2003
Neisseria meningitidis (Total Isolates = 27)							
Neisseria meningitidis	10	0.015	0.004 - 0.015	Agar dilution	Non-US	Woodcock et al.	1997
Neisseria meningitidis	17	0.016	0.008 - 0.016	Agar dilution	US & Non-US	FungTomc et al.	2000
Pantoea agglomerans (Total Isolates = 34)							
Pantoea agglomerans	16	2.0	0.004 – 2.0	Agar dilution	Non-US	Bauernfeind	1997
Pantoea agglomerans	18	0.25	0.03 - 0.25	Broth dilution	US	TDOC-0000208	2003
Proteus vulgaris (Total Isolates = 109)							
Proteus vulgaris	18	1.0	0.06 – 2.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Proteus vulgaris	24	0.25	0.0009 – 4.0	Agar dilution	Non-US	Dalhoff et al.	1996
Proteus vulgaris	15	0.25	0.06 - 0.50	Agar dilution	Non-US	Woodcock et al.	1997
Proteus vulgaris	35	0.50	0.06 - 0.50	Agar dilution	Non-US	Bauernfeind	1997
Proteus vulgaris	17	0.5	0.12 - 1.0	Agar dilution	Non-US	Soussy CJ et al.	2003
Serratia liquefaciens (Total Isolates = 41)							
Serratia liquefaciens	32	1.0	0.03 - 32	Agar dilution	Non-US	Bauernfeind	1997
Serratia liquefaciens	4	2.0	0.03 - 16	Agar dilution	Non-US	Woodcock et al.	1997
Serratia liquefaciens	5	--	0.06 - 0.50	Broth dilution	US	TDOC-0000208	2003
Serratia marcescens (Total Isolates = 177)							
Serratia marcescens	18	1.0	0.25 – 1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Serratia marcescens	33	1.0	0.03 - 2.0	Broth dilution	US	TDOC-0000208	2003
Serratia marcescens	10	0.380	--	E test	US	Kowalski RP et al.	2003
Serratia marcescens	18	0.50	0.06 – 1.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Serratia marcescens	15	2.0	0.03 - 16	Agar dilution	Non-US	Woodcock et al.	1997
Serratia marcescens	61	4.0	0.063 - 16	Agar dilution	Non-US	Soussy CJ et al.	2003
Serratia marcescens	22	2.0	0.25 - 8	Agar dilution	Non-US	Otani T et al.	2003
Stenotrophomonas maltophilia (Total Isolates = 179)							
Stenotrophomonas maltophilia	17	0.50	0.031 - 4.0	Agar dilution	Non-US	Dalhoff et al.	1996
Stenotrophomonas maltophilia	13	2.0	0.06 - 2.0	Agar dilution	Non-US	Woodcock et al.	1997
Stenotrophomonas maltophilia	18	1.0	0.12 - 4.0	Agar dilution	US & Non-US	FungTomc et al.	2000
Stenotrophomonas maltophilia	23	2.0	0.25 - 8.0	Broth dilution	US	TDOC-0000208	2003
Stenotrophomonas maltophilia	47	2.0	≤0.01 - 32	Agar dilution	Non-US	Canton R et al.	2003
Stenotrophomonas maltophilia	38	0.38	0.032 - 16	Broth dilution	Non-US	Soussy CJ et al.	2003
Stenotrophomonas maltophilia	20	4.0	0.12 - 8	Broth dilution	Non-US	Bonaventura et al.	2004
Stenotrophomonas maltophilia	3	--	0.5 - 2.0	Agar dilution	Non-US	Ba BB et al.	2004

Table 2: Moxifloxacin Activity Against Anaerobic Microorganisms

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Bacteroides vulgatus (Total Isolates=29)							
Bacteroides vulgatus	29	1.0	0.12-32	Broth dilution	US & Non-US	Schaumann et al.	2000
Clostridium perfringens (Total Isolates = 178)							
Clostridium perfringens	40	0.5	0.12 - 2.0	Agar dilution	US	Hecht DW et al.	2003
Clostridium perfringens	18	0.50	0.50 - 0.50	Agar dilution	US & Non-US	FungTome et al.	2000
Clostridium perfringens	11	0.50	0.25 - 0.50	Agar dilution	Not available	Ednie et al.	2002
Clostridium perfringens	20	0.50	Not available	Agar dilution	Not available	Ednie et al.	2002
Clostridium perfringens	25	0.50	0.25 - 1.0	Agar dilution	Non-US	Appelbaum et al.	2002
Clostridium perfringens	8	--	0.12 - 1.0	Agar dilution	Non-US	Soussy CJ et al.	2003
Clostridium perfringens	25	0.5	0.25 - 1.0	Agar dilution	Unknown	Peric M et al.	2004
Peptostreptococcus anaerobius (Total Isolates = 35)							
Peptostreptococcus anaerobius	4	--	0.12-1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus anaerobius	10	8.0	0.25 - 16	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus anaerobius	1	--	0.25 - 0.25	Agar dilution	US	Credito KL et al.	2003
Peptostreptococcus anaerobius	20	0.25	0.12 - 0.25	Agar dilution	US	Ednie L et al.	2007
Peptostreptococcus asacchrolyticus (Total Isolates = 16)							
Peptostreptococcus asacchrolyticus	12	1.0	<=0.25 - 4.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus asacchrolyticus	1	--	0.12 - 0.25	Agar dilution	US	Credito KL et al.	2003
Peptostreptococcus asacchrolyticus	15	0.25	≤0.015 - 1.0	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus magnus (Total Isolates = 10)							
Peptostreptococcus magnus	10	0.25	0.06 - 0.5	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus micros (Total Isolates = 23)							
Peptostreptococcus micros	11	0.5	<=0.004-0.5	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus micros	12	2.0	0.12 - 4.0	Agar dilution	US	Hecht DW et al.	2003
Peptostreptococcus prevotii (Total Isolates = 21)							
Peptostreptococcus prevotii	12	1.0	0.12 - 2.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008
Peptostreptococcus prevotii	9	--	0.12 - 1.0	Agar dilution	US	Hecht DW et al.	2003
Porphyromonas gingivalis (Total Isolates = 35)							
Porphyromonas gingivalis	35	0.50	0.06 - 0.50	Broth dilution	Non-US	Milazzo et al.	2002
Porphyromonas spp. (Total Isolates = 11)							
Porphyromonas spp.	11	0.25	≤0.15 - 0.5	Agar dilution	US	Hecht DW et al.	2003
Prevotella buccae (Total Isolates = 43)							
Prevotella buccae	20	1.0	0.5 - 4.0	Agar dilution	US	Ednie L et al.	2007
Prevotella buccae	12	0.5	0.25 - 0.5	Agar dilution	US	Hecht DW et al.	2003
Prevotella buccae	11	0.5	0.25 - 0.5	Agar dilution	Unknown	Peric M et al.	2004
Prevotella corporis (Total Isolates = 12)							
Prevotella corporis	12	1.0	0.5 - 1.0	Agar dilution	Unknown	Peric M et al.	2004
Prevotella melanogenica (Total Isolates = 5)							
Prevotella melanogenica	5	--	0.50 – 1.0	Broth dilution	US	Alcon Studies 2005 to 2008	2005 2008

Table 3: Moxifloxacin Activity Against Mycobacteria

Bacterial Species	N	MIC_{90} (µg/ml)	MIC Range (µg/ml)	Test Method	Geographic Source	Reference	Year
Mycobacterium tuberculosis (Total Isolates = 439)							
Mycobacterium tuberculosis	243	0.5	0.06 – 8.0	Agar dilution	Non-US	Rodriguez et al.	2002
Mycobacterium tuberculosis	84	0.5	0.5 - 1.0	Agar dilution	Non-US	Tortoli et al.	2004
Mycobacterium tuberculosis	112	0.5	0.5 – 2.0	Broth dilution	Non-US	Kam et al.	2006
Atypical *Mycobacterium* (169)							
Mycobacterium avium (Total Isolates = 12)							
Mycobacterium avium	12	1.0	<0.25 - 1.0	Broth dilution	Non-US	Gillespie & Billington	1999
Mycobacterium kansasii (Total Isolates =104)							
Mycobacterium kansasii	104	0.12	0.006-1.0	Broth dilution	Non-US	Guna et al.	2005
Mycobacterium marinum (Total Isolates = 53)							
Mycobacterium marinum	53	1.0	0.25 - 4.0	Agar dilution	Non-US	Aubry et al.	2000

The referenced studies show that moxifloxacin is active against a wide variety of pathogens, including those that the Applicant suggests may be potential pathogens in cases of bacterial conjunctivitis, including isolates that are non-susceptible to other quinolones. Recent studies [Ohnsman 2007] suggest that moxifloxacin is also active, in vitro, against isolates most commonly associated with bacterial conjunctivitis, including *Haemophilus influenzae*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Propionibacterium acnes*, although some studies have suggested reduced susceptibility to moxifloxacin in isolates of *S. epidermidis*, due to in gyrA and parC mutations [Betanzos 2009]. Activity of moxifloxacin against these pathogens (pathogens most commonly associated with bacterial conjunctivitis) is also demonstrated in comparisons of isolates collected in clinical trials of VIGAMOX (2001-2002) and isolates collected in the trials performed to support this Application (2005-2007). These data are summarized in Tables 4 - 7. Of the four species analyzed, only isolates of *S. epidermidis* demonstrated reduced susceptibility to moxifloxacin in the more recent trials.

Table 4: Comparison of Antibiotic Resistance in Ocular Isolates of *Streptococcus pneumoniae*

Streptococcus pneumoniae	**2001-2002**		**2005-2007**	
Total Isolates	**N =159**	**% Resistant**	**N =53**	**% Resistant**
Antibiotic (resistance breakpoint)				
Penicillin-resistant (>0.5 µg/ml)	11	6.9%	1	1.9%
Erythromycin-resistant (>0.5 µg/ml)	53	33%	9	17%
Clindamycin-resistant (>1.0 µg/ml)	9	5.7%	0	0.0%
Tetracycline-resistant (>2.0 µg/ml)	36	23%	3	5.7%
Trimethoprim-resistant (>8.0 µg/ml)	54	34%	7	13%
Sulfamethoxazole-resistant (>128 µg/ml)	73	46%	9	17%
Ciprofloxacin-resistant (>2.0 µg/ml)	1	0.6%	0	0.0%
Moxifloxacin-resistant (>2.0 µg/ml)	0	0.0%	0	0.0%
Moxifloxacin-resistant (>0.5 µg/ml)	0	0.0%	0	0.0%

Source: Table 2.7.2.4.-5; this submission

Table 5: Comparison of Antibiotic Resistance in Ocular Isolates of *Haemophilus influenzae*

Haemophilus influenzae	**2001-2002**		**2005-2007**	
Total Isolates	**N =214**	**% Resistant**	**N =117**	**% Resistant**
Antibiotic (resistance breakpoint)				
Ampicillin-resistant (>2.0 µg/ml)	83	39%	38	33%
Tetracycline-resistant (>4.0 µg/ml)	1	0.5%	2	1.7%
Trimethoprim-resistant (>16 µg/ml)	69	32%	27	23%
Ciprofloxacin-resistant (>0.13 µg/ml)	1	0.5%	0	0.0%
Moxifloxacin-resistant (>0.25 µg/ml)	0	0.0%	0	0.0%

Source: Table 2.7.2.4.-6; this submission

Table 6: Comparison of Antibiotic Resistance in Ocular Isolates of *Staphylococcus aureus*

Staphylococcus aureus	**2001-2002**		**2005-2007**	
Total Isolates	**N = 122**	**% Resistant**	**N = 21**	**% Resistant**
Antibiotic (resistance breakpoint)				
Oxacillin-resistant (>2μg/ml)	14	12%	2	9.5%
Erythromycin-resistant (>2.0 μg/ml)	31	25%	9	43%
Clindamycin-resistant (>1.0 μg/ml)	9	7.4%	1	4.8%
Tobramycin-resistant (>2.0 μg/ml)	19	16%	0	0.0%
Gentamicin-resistant (>2.0 μg/ml)	8	6.6%	0	0.0%
Neomycin-resistant (>8.0 μg/ml)	18	15%	3	14%
Tetracycline-resistant (>2.0 μg/ml)	8	6.6%	1	4.8%
Trimethoprim-resistant (>8.0 μg/ml)	24	20%	1	4.8%
Sulfamethoxazole-resistant (>128 μg/ml)	93	76%	16	76%
Ciprofloxacin-resistant (>2.0 μg/ml)	20	16.4%	1	4.8%
Moxifloxacin-resistant (>2.0 μg/ml)	11	9.0%	1	4.8%
Moxifloxacin-resistant (>0.5 μg/ml)	20	16%	1	4.8%

Source: Table 2.7.2.4.-7; this submission

Table 7: Comparison of Antibiotic Resistance in Ocular Isolates of *Staphylococcus epidermidis*

Staphylococcus epidermidis	**2001-2002**		**2005-2007**	
Total Isolates	**N = 248**	**% Resistant**	**N =65**	**% Resistant**
Antibiotic (resistance breakpoint)				
Oxacillinresistant (>0.25μg/ml)	132	53%	32	49%
Erythromycin-resistant (>2.0 μg/ml)	164	66%	37	57%
Clindamycin-resistant (>1.0 μg/ml)	37	15%	13	20%
Tobramycin-resistant (>2.0 μg/ml)	48	19%	10	15%
Gentamicin-resistant (>2.0 μg/ml)	19	7.7%	3	4.6%
Neomycin-resistant (>4.0 μg/ml)	34	14%	8	12%
Tetracycline-resistant (>2.0 μg/ml)	37	15%	12	19%
Trimethoprim-resistant (>8.0 μg/ml)	32	13%	7	11%
Sulfamethoxazole-resistant (>128 μg/ml)	229	92%	52	80%
Ciprofloxacin-resistant (>2.0 μg/ml)	25	10%	11	17%
Moxifloxacin-resistant (>2.0 μg/ml)	4	1.6%	3	4.6%
Moxifloxacin-resistant (≥0.5 μg/ml)	25	10%	11	17%

Source: Table 2.7.2.4.-8; this submission

Data regarding moxifloxacin activity against isolates commonly associated with bacterial conjunctivitis, recovered from Study Eyes at the baseline visit in the two Phase 3 clinical trials, is summarized in Table 8. Although MIC_{90} values against all of the principle pathogens indicates activity of moxifloxacin in vitro (no data is available for *Chlamydia trachomatis*), the calculated MIC range for isolates of *Staphylococcus epidermidis* suggests a proportion of isolates with reduced susceptibility to the antimicrobial.

Table 8: Moxifloxacin in vitro activity against pre-therapy isolates collected in Phase 3 Clinical Trials (Study Eye, MBITT population)

Organism	Study C-04-38 (MBITT)			Study C-04-40 (MBITT)		
	n	MIC_{range} mcg/ml	MIC_{90} mcg/ml	n	MIC_{range} mcg/ml	MIC_{90} mcg/ml
Staphylococcus aureus	11	0.03-0.12	0.06	14	0.03-2	2
Staphylococcus epidermidis	34	0.06-8	1	51	0.03-32	1
Streptococcus pneumoniae	36	0.015-0.12	0.12	0	n/a	n/a
Haemophilus influenzae	59	≤0.004-0.06	0.03	0	n/a	n/a
Propionibacterium acnes	71	≤0.002-0.125	0.064 (2)	5	n/a (1)	n/a (1)
Chlamydia trachomatis	0	n/a	n/a	16	n/a (1)	n/a (1)

Sources: Document TDOC-0008134, Table 4.9.-1; TDOC-0008133, Table 4.9.-1
Notes: (1) susceptibility testing not performed, (2) test performed by (b) (4)-approved agar dilution method (all other susceptibility testing performed by (b) (4)-approved broth-dilution method

The Applicant has submitted no new information regarding the bactericidal activity of moxifloxacin and no new studies of time-kill kinetics against ophthalmologic pathogens. The Applicant has referenced NDA 21-598 with regard to these studies of moxifloxacin ophthalmic solution.

The concentration of moxifloxacin in Moxifloxacin AF Ophthalmic Solution is 5 mg/mL. At the recommended dose (0.50 mg moxifloxacin in 2 drops) initial exposure of the antibiotic is in significant excess, compared to the MIC_{range} of all pathogens listed in the proposed label.

In Summary:

Moxifloxacin is active, in vitro, against a wide variety of bacterial pathogens, including Gram-positive and Gram-negative bacteria, certain obligate anaerobes, and some mycobacterial species. Moxifloxacin in vitro antibacterial activity includes some isolates resistant to other fluoroquinolones (e.g. ciprofloxacin). Summary data compiled by the Applicant to support a list of potential ophthalmic pathogens with in vitro susceptibility to moxifloxacin ("second list" organisms), included only those species with moxifloxacin MIC_{90} values ≤ 2 mcg/ml, and only those species not sufficiently characterized in data compiled from the two large clinical trials. Moxifloxacin was active against pre-therapy isolates of the principle pathogens associated with bacterial conjunctivitis, collected during Phase 3 clinical trials, including isolates of *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *H. influenzae*, and *P. acnes*. Reduced moxifloxacin activity was noted in some isolates of *S. epidermidis*. The concentration of moxifloxacin in Moxifloxacin AF Ophthalmic Solution is 5 mg/mL. At the recommended dose (0.50 mg moxifloxacin in 2 drops) initial exposure of the antibiotic is in significant excess, compared to the MIC_{range} of all pathogens listed in the proposed label.

Antimicrobial Spectrum of Activity Studies ~ Conclusions:

Moxifloxacin demonstrates in vitro activity against the primary pathogens associated with bacterial conjunctivitis and against a wide variety of other bacteria that may represent potential ophthalmic pathogens, including some isolates that are non-susceptible to other fluoroquinolones. In vitro testing of these species, both during the Phase 3 trials reported in this Application and as reported in supportive data submitted by the Applicant, supports the inclusion of the species requested in the proposed label.

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 submitted no new information regarding mechanisms of moxifloxacin resistance or the development of moxifloxacin-resistance in bacterial isolates commonly associated with conjunctival infections.

No development of resistance to moxifloxacin was noted in the two Phase 3 clinical trials.

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*.

Resistance Studies ~ Conclusions:

The Applicant has submitted no new information regarding the mechanisms of resistance to moxifloxacin among isolates commonly associated with bacterial conjunctivitis. Recent studies, including literature surveys compiled by the Applicant, suggest decreased susceptibility to moxifloxacin in certain bacterial species, including *Staphylococcus epidermidis* and some *Corynebacterium* species. No development of resistance to moxifloxacin was noted in the two clinical trials of Moxifloxacin AF Ophthalmic Solution.

HUMAN AND ANIMAL STUDIES

ANIMAL EFFICACY STUDIES

The Applicant has submitted data from a study designed to investigate the in vivo activity of Moxifloxacin AF against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Report TDOC-00200; Evaluation of Moxifloxacin Formulations for the Treatment and Prevention of Experimental (b) (4)). The study, conducted at the Louisiana State University Health Sciences Center (New Orleans, LA) in 2004, tested three formulations of moxifloxacin (VIGAMOX, moxifloxacin with xanthan, and (b) (4)) in animal models of *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections, including both prophylactic and therapeutic models. Levofloxacin and CILOXAN were included as comparators.

In these experiments, bacteria were grown overnight in nutrient broth, subcultured and incubated until an approximate 10^8 CFU /ml inoculum was prepared. Bacterial density was determined by subculture to sold media. New Zealand White rabbits were intrastromally injected with 10 mcl of the log-phase bacterial culture, and were topically treated. Bacterial load was determined by dissection of corneas, homogenation in sterile phosphate buffered saline, and inoculation to solid media. Tested isolates included *S. aureus* MCC30155 (resistant to ciprofloxacin and oxacillin), *S. aureus* strain 8325-4, and *P. aeruginosa* ATCC 27853. The MIC values for the tested bacteria are summarized in Table 9. Topical treatments (as drops) contained 50 uL of antibiotic solution, equivalent to 0.25 mg moxifloxacin.

Table 9: Minimal Inhibitory Concentration (MIC) of Antibiotics Used in Keratitis Studies

Bacteria	Minimal Inhibitory Concentration (µg/ml)				
	Oxacillin	Ciprofloxacin	Ofloxacin	Levofloxacin	Moxifloxacin
***S. aureus* 8325-4**	Sensitive	0.13	0.25	0.13	0.03
***S. aureus* 30155**	64	128	32	8.0	2.0
***P. aeruginosa* 27853**	N/A	0.13	1.0	0.5	1.0

Source: This submission; Report TDOC-00200, Table 3.2.-1

The results of the investigations are summarized in Tables 10 through 12.

In the early therapy studies (log growth phase), Moxifloxacin AF was more effective than VIGAMOX at decreasing the load of the quinolone-susceptible *S. aureus* strain, and comparable to all comparators against the quinolone-resistant *S. aureus* strain. In the late therapy studies (stationary phase), Moxifloxacin AF was comparable to all moxifloxacin preparations, but more effective than levofloxacin. Against *P. aeruginosa* (treated every hour from 24 to 26 hours, 3 drops total), Moxifloxacin AF treatment was similar to other moxifloxacin preparations in reducing corneal bacterial load, but significantly less active than linezolid.

Table 10: Early (4-9 hours PI) therapy of *S. aureus* keratitis

Antibiotic Formulation	Experiment #1		Experiment #2	
	Log CFU/Cornea	Log Reduction [a]	Log CFU/Cornea	Log Reduction [a]
VIGAMOX (0.5%)	2.35 ± 0.75 [c]	4.65	1.14 ± 0.75 [f]	5.91
Moxifloxacin AF (0.5%)	0.00 ± 0.00 [c, d]	7.00	1.80 ± 0.74 [f]	5.25
Moxifloxacin Ointment (0.5%)	1.10 ± 0.70 [d]	5.90	0.90 ± 0.57 [f]	6.15
Levofloxacin (1.5%)	1.15 ± 1.15 [d]	5.85	1.40 ± 0.76 [f]	6.01
Untreated	7.00 ± 0.26 [b]	--	7.05 ± 0.24 [e]	--

[a] Reduction in log CFU/cornea relative to the untreated group.
[b] Significantly different than all antibiotic-treated groups ($P \leq 0.0004$).
[c] Significantly different from each other ($P = 0.0382$).
[d] Not significantly different than each other ($P = 0.2642$).
[e] Significantly different than all antibiotic-treated groups ($P \leq 0.00001$).
[f] Not significantly different than each other ($P = 0.3154$).
Source: This submission; Report TDOC-00200, Table 4.1.-1

Table 11: Late (10-15 hours PI) therapy of *S. aureus* keratitis

Antibiotic Formulation	10-15 hrs PI	
	Log CFU/Cornea	Log Reduction [a]
VIGAMOX (0.5%)	6.29 ± 0.17 [b]	0.82
Moxifloxacin AF (0.5%)	6.00 ± 0.22 [b]	1.11
Moxifloxacin Ointment (0.5%)	6.46 ± 0.08 [b]	0.65
Levofloxacin (1.5%)	6.52 ± 0.20 [c]	0.59
Untreated	7.11 ± 0.27	--

[a] Reduction in log CFU/cornea relative to the untreated group.
[b] Significantly different than the untreated group ($P \leq 0.0445$).
[c] Not significantly different than the untreated group ($P = 0.0721$).
Source: This submission; Report TDOC-00200, Table 4.1.-2

Table 12: Treatment of *Pseudomonas aeruginosa* Keratitis

Antibiotic Formulation	Log CFU/Cornea	Log Reduction [a]
VIGAMOX (0.5%)	5.78 ± 0.27 [e, f, g]	1.85
Moxifloxacin AF (0.5%)	5.23 ± 0.36 [e, f, g]	2.40
Moxifloxacin Ointment (0.5%)	6.20 ± 0.30 [d, e]	1.43
Levofloxacin (1.5%)	2.41 ± 0.49 [c]	5.22
CILOXAN (0.3%)	5.02 ± 0.37 [d, f]	2.61
Untreated	7.63 ± 0.05 [b]	--

[a] Reduction in log CFU/cornea relative to the untreated group.
[b] Significantly different than antibiotic-treated groups ($P \leq 0.0063$).
[c] Significantly lower than all other groups ($P \leq 0.0001$).
[d] Significantly different from each other ($P = 0.02$).
[e] Moxifloxacin ointment group was not significantly different from the groups treated with VIGAMOX ($P = 0.3789$) or moxifloxacin AF ($P = 0.0503$).
[f] Not significantly different from each other ($P \geq 0.1147$).
[g] Not significantly different from each other ($P = 0.2453$).
Source: This submission; Report TDOC-00200, Table 4.2.-1

In the prophylaxis models (Tables 13 and 14), Moxifloxacin AF was more effective than levofloxacin at limiting growth of *S. aureus* 30155 (resistant to quinolones) when animals were treated 30 minutes prior to bacterial injection, but similar to levofloxacin (and all comparators) when treatment was at 3 hours prior to injection. Against *S. aureus* 8325-4 (susceptible to quinolones), Moxifloxacin AF was more effective as a prophylactic treatment than levofloxacin but statistically similar to other moxifloxacin preparations. Against *P. aeruginosa,* treated 3 hours prior to bacterial injection, Moxifloxacin AF was more effective than VIGAMOX, but less effective than CILOXAN and levofloxacin.

Table 13: Prophylactic treatment of *S. aureus* keratitis

Antibiotic Formulation	Log CFU/Cornea		
	S. aureus 30155		*S. aureus* 8325-4
	30 min [a]	3 hours [a]	8 hours [a]
VIGAMOX (0.5%)	2.95 ± 0.33 [b]	5.41 ± 0.18 [b]	3.33 ± 1.06 [b, g]
Moxifloxacin AF (0.5%)	2.35 ± 0.28 [b]	5.03 ± 0.15 [b]	2.12 ± 1.01 [b, e, g]
Moxifloxacin Ointment (0.5%)	2.58 ± 0.38 [b]	5.19 ± 0.09 [b]	2.89 ± 1.06 [b, e, g]
Levofloxacin (1.5%)	4.89 ± 0.20 [c]	5.09 ± 0.17 [b]	4.69 ± 0.33 [f, g]
Untreated	5.02 ± 0.19 [c, d]	5.00 ± 0.13 [b]	5.73 ± 0.11 [d, f]

[a] Time prior to injection of bacterial inoculum.
[b] No significant difference between groups ($P \geq 0.0550$).
[c] Not significantly different for each other ($P \geq 0.05$)
[d] Significantly different than the antibiotic-treated groups ($P \leq 0.010$).
[e] Significantly different from each other ($P \leq 0.030$).
[f] Not significantly different from each other ($P = 0.2265$).
[g] Significantly different from each other ($P \geq 0.045$).
Source: This submission; Report TDOC-00200, Table 4.3.-1

Table 14: Prophylactic treatment of *P. aeruginosa* Keratitis

Antibiotic Formulation	Log CFU/Cornea
	3 hours [a]
VIGAMOX (0.5%)	5.20 ± 0.14 [c, e, f]
Moxifloxacin AF (0.5%)	4.26 ± 0.41 [b, f, g]
Moxifloxacin Ointment (0.5%)	5.03 ± 0.13 [c, , e, g]
Levofloxacin (1.5%)	2.52 ± 0.40 [b ,d, f]
CILOXAN (0.3%)	2.50 ± 0.43 [b, d, f]
Untreated	5.17 ± 0.21 [b, c]

[a] Time prior to injection of bacterial inoculum.
[b] Untreated group was significantly higher than moxifloxacin AF, levofloxacin (1.5%), and CILOXAN groups ($P \leq 0.0252$).
[c] Not significantly different from each other ($P \geq 0.7076$).
[d] Not significantly different from each other ($P = 0.9512$), but were significantly different from all other groups ($P \leq 0.0002$).
[e] Not significantly different from each other ($P = 0.6629$).
[f] Moxifloxacin AF was significantly different from the CILOXAN, levofloxacin (1.5%), and VIGAMOX groups ($P \leq 0.0221$).
[g] Not significantly different from each other ($P = 0.0541$).
Source: This submission; Report TDOC-00200, Table 4.3.-2

In summary:

The Applicant has submitted a report (TDOC-00200) from a study designed to investigate the in vivo efficacy of Moxifloxacin AF Ophthalmic Solution, compared to VIGAMOX, levofloxacin, and CILOXAN (only used as a comparator in tests against *Pseudomonas aeruginosa*). The studies suggest that Moxifloxacin AF is more effective in early therapy treatment than VIGAMOX against *S. aureus* isolates susceptible to quinolones, similar to VIGAMOX but more effective than levofloxacin against *S. aureus* in late stage therapy models. No statistical difference was noted between comparators in treating isolates of quinolone-resistant *S. aureus* in early stage models. Against *Pseudomonas aeruginosa*, all moxifloxacin preparations were similarly effective, and all were less effective than levofloxacin. In prophylaxis models, all moxifloxacin preparations behaved similarly against *S. aureus* infection in both 30-minute and 3-hour pre-infection treatment regimens. Against *P. aeruginosa*, Moxifloxacin AF prophylaxis was more effective than VIGAMOX, but less effective than levofloxacin or CILOXAN.

Animal Efficacy Studies ~ Conclusions:

Moxifloxacin AF is effective at reducing bacterial counts (quinolone-susceptible and –resistant *S. aureus*, and *P. aeruginosa*), relative to untreated controls, in the corneas of New Zealand white rabbits, in both late- and early-stage therapy. Moxifloxacin AF is also effective, relative to untreated controls, when administered prior to infection (prophylactically) at 30 minutes pre-infection with quinolone-susceptible *S. aureus*, 8 hours pre-infection with quinolone-resistant *S. aureus,* and 3 hours pre-infection with *P. aeruginosa*. Moxifloxacin was statistically similar to the untreated control in a prophylaxis administered 3 hours prior to infection with quinolone-susceptible *S. aureus*.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The Applicant has submitted data from two studies designed to investigate the pharmacokinetics of Moxifloxacin AF Ophthalmic Solution in tear film and aqueous humor.

In the first experiment (Alcon Report EM:005:00735:1104), tear film concentrations of Moxifloxacin AF were compared to concentrations of VIGAMOX in New Zealand white rabbits. Samples were taken at 1, 5, 10, 30, and 60 after a single dose. Tear film concentrations of Moxifloxacin AF were higher at all sampling points, but only marginally higher in the 60 minute sample (difference decreasing over time) (Table 15). The Applicant determined AUC values for both treatments. The $AUC_{0\text{-}10\ min}$ was significantly higher for Moxifloxacin AF than VIGAMOX (Table 16).

Table 15: Mean concentration ± SD of moxifloxacin in tear film following administration of Moxifloxacin AF Ophthalmic Solution or VIGAMOX®

Test article	Sampling time (min)	Concentration (µg/mL)
Moxifloxacin AF Ophthalmic Solution	1	3656 ± 1292
	5	2035 ± 273
	10	122 ± 120
	30	13.59 ± 9.17
	60	4.98 ± 3.99
VIGAMOX®	1	3621 ± 1000
	5	258 ± 153
	10	17.8 ± 9.1
	30	3.56 ± 2.45
	60	3.02 ± 2.82

Source: This submission, Table 2.6.4.10-2

Table 16: $AUC_{0\text{-}60}$ and statistical comparison of moxifloxacin in tear film following administration of Moxifloxacin AF Ophthalmic Solution or VIGAMOX®

Moxifloxacin AF Ophthalmic Solution			**VIGAMOX®**		
$AUC_{0\text{-}60\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}60\ min}$)	dfSE ($AUC_{0\text{-}60\ min}$)	$AUC_{0\text{-}60\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}60\ min}$)	dfSE ($AUC_{0\text{-}60\ min}$)
20240	1376	13	10571	1161	5
df dif Moxifloxacin AF - VIGAMOX® = 16			t = 5,371	p<0.01	

SE = standard error
df = degrees of freedom

Source: This submission, Table 2.6.4.10-3

In the second study (Alcon Report EM:002:00735:0804), concentrations of Moxifloxacin AF and VIGAMOX were determined in pigmented New Zealand white rabbit aqueous humor at various sampling points (15, 30, 60, and 120 minutes) following a single dose of antibiotic. Concentrations of Moxifloxacin AF were higher than those of VIGAMOX at all sampling points (Table 17), and the calculated $AUC_{0\text{-}12\ min}$ was statistically higher for the Moxifloxacin AF treated animals (Table 18).

Table 17: Mean concentration ± SD of moxifloxacin in aqueous humor following administration of Moxifloxacin AF Ophthalmic Solution of VIGAMOX®

Test article	Sampling time (min)	Concentration (µg/mL)
Moxifloxacin AF Ophthalmic Solution	15	2.21 ± 0.69
	30	4.74 ± 0.70
	60	2.54 ± 0.77
	120	0.78 ± 0.30
VIGAMOX®	15	0.89 ± 0.37
	30	1.61 ± 0.71
	60	1.18 ± 0.49
	120	0.49 ± 0.03

Source: This submission, Table 2.6.4.10-4

Table 18: AUC0-120 and statistical comparison of moxifloxacin in aqueous humor following administration of Moxifloxacin AF Ophthalmic Solution or VIGAMOX®

Moxifloxacin AF Ophthalmic Solution			**VIGAMOX®**		
$AUC_{0\text{-}120\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}120\ min}$)	dfSE ($AUC_{0\text{-}120\ min}$)	$AUC_{0\text{-}120\ min}$ (ug*min/mL)	SE ($AUC_{0\text{-}120\ min}$)	dfSE ($AUC_{0\text{-}120\ min}$)
277	17	9	118	11	10
df dif Moxifloxacin AF - VIGAMOX® = 16			$t = 7.973$	$p<0.01$	

SE = standard error
df = degrees of freedom
Source: This submission, Table 2.6.4.10-5

Study C-05-15 was designed as a single-center, double-masked multi-dose study in healthy subjects to evaluate the steady-state plasma pharmacokinetics of moxifloxacin, following bilateral, topical administration of Moxifloxacin AF Ophthalmic Solution 0.5% in healthy adult subjects. The study enrolled 30 subjects, 20 of whom received that active treatment and 10 of whom received vehicle. Subjects were dosed twice daily (every 12 hours) for four days, and a last dose was administered on the morning of Day 5. Plasma samples were collected prior to the morning dose on Days 2 through 5. Serial samples were collected on Day 5 (0.25, 0.5,1,2,4,6,8,12 hours), on Day 6 (at 24 hours after last dose), and Day 7 (48 hours after last dose).

Mean peak moxifloxacin concentration was observed after one hour, and mean steady-state concentrations were achieved by Day 3. At C_{max}, plasma levels of Moxifloxacin AF Ophthalmic Solution were significantly lower than that of VIGAMOX (0.977 ng/ml, and 2.70 ng/ml, respectively). Data from Study C-05-15 are summarized in Table 19.

Table 19: Moxifloxacin steady-state plasma pharmacokinetic parameters after administration of Moxifloxacin AF Ophthalmic Solution (two times a day) and VIGAMOX® (three times a day)

Moxifloxacin AF Ophthalmic Solution BID (C-05-15)					
	C_{max} (ng/mL)	**T_{max} (h)**	**AUC_{0-8} (ng*h/mL)**	**AUC_{0-12} (ng*h/mL)**	**$t_{1/2}$ (h)**
Mean	0.977	0.88	6.08	8.17	16.6
SD	0.673	0.55	4.05	5.31	5.5
Min	0.267	0.25	1.77	2.33	7.6
Max	3.19	2.00	17.7	22.8	27.3
N	20	20	20	20	20
VIGAMOX® TID (C-01-48)					
	C_{max} (ng/mL)	**T_{max} (h)**	**AUC_{0-8} (ng*h/mL)**	**AUC_{0-12} (ng*h/mL)**	**$t_{1/2}$ (h)**
Mean	2.70	0.57	15.0	ND	13.1
SD	1.29	0.40	5.3	ND	3.3
Min	0.98	0.23	8.1	ND	7.0
Max	5.95	2.00	25.1	ND	19.7
N	21	21	19	ND	19

ND = Not determined
Source: This submission, Table 2.7.2.3.-1

In summary:

In a study designed to investigate the concentration of Moxifloxacin AF in tear film, New Zealand white rabbits were dosed once with Moxifloxacin AF or VIGAMOX. Moxifloxacin AF concentrations exceeded those of VIGAMOX at all sampling times, although the difference decreased over time. $AUC_{0-16\ min}$ for Moxifloxacin AF was significantly higher than that of VIGAMOX. Similarly, in a study designed to investigate the concentration of Moxifloxacin AF in the aqueous humor of New Zealand white rabbits, following a single administration, Moxifloxacin AF concentration exceeded that of VIGAMOX at each sampling point. $AUC_{0-120\ min}$ was significantly higher for the Moxifloxacin AF-treated animals than for the VIGAMOX-treated group. Results from Study C-05-15 (a Phase 1 clinical trial, enrolling 30 subjects) indicate rapid absorption of moxifloxacin, with C_{max} (0.977 ng/ml) attained within one hour of dosing. Steady-state concentrations were attained by Day 3 of a twice-daily (every 12 hours) dosing regimen. Systemic exposure over the 12-hour dosing interval (AUC_{0-12}) averaged 8.17 ± 5.31 ng*h/mL.

Pharmacokinetic / Pharmacodynamic Studies ~ Conclusions:

Experiments in New Zealand white rabbits suggest that Moxifloxacin AF attains high concentrations in both tear film and aqueous humor following a single dose of the antimicrobial, and that levels in both fluids exceed those of VIGAMOX administered identically. Clinical trials in healthy human subjects suggest that Moxifloxacin AF administration over a dosing interval results in lower systemic exposure compared to that of VIGAMOX.

CLINICAL TRIALS

The Applicant conducted two Phase 3 trials in support of this NDA. Both were designed as prospective, multicenter, double-masked, parallel group studies. Study C-04-38 was conducted in the U.S. and was designed to demonstrate superiority over vehicle. Subjects received a three-day course of either one drop of Moxifloxacin AF Ophthalmic Solution two times a day in both eyes, or one drop of vehicle two times per day in both eyes. Study C-04-40 was conducted in India and was designed to demonstrate non-inferiority to VIGAMOX. Subjects received a three-day course of either one drop of Moxifloxacin two times per day in both eyes (and one drop of vehicle in both eyes, delivered mid-day, to protect masking), or one drop of VIGAMOX three time per day in both eyes.

Participants included subjects one month of age or older with a diagnosis of bacterial conjunctivitis based on clinical observation. The major exclusion and inclusion criteria were similar for both trials. The principle evaluation visits included a Baseline Visit (Day 1), an End of Therapy Visit (Day 4, 12-48 hours after last dose), and a Test of Cure Visit (Day 7, 60-96 hours after last dose). The primary efficacy endpoints for both studies were clinical cure (complete resolution bulbar conjunctival injection and conjunctival discharge/exudate) and microbiological success (eradication of all pathogens identified at the Baseline Visit). "Microbiology treatment failure" was defined as any one of the following, 1) persistence of the pre-therapy pathogen(s), or presumed persistence if no specimen is collected in a patient with clinical signs; 2) reinfection (recovery of a pathogen at the Test of Cure Visit that was not present at the Baseline Visit), and 3) early discontinuation due to treatment failure (regardless of specimen culture results).

The study parameters for C-04-48 and C-04-40 are summarized in Table 20.

Table 20: Study Parameters for C-04-38 and C-04-40

Study	C-04-38	C-04-40
Location	U.S.	India
Objective	Demonstration of the superiority of Moxifloxacin AF to Vehicle for the treatment of bacterial conjunctivitis	Demonstration of the non-inferiority of Moxifloxacin AF to VIGAMOX® for the treatment of bacterial conjunctivitis
Treatment Groups	Moxifloxacin AF Ophthalmic Solution Vehicle	Moxifloxacin AF Ophthalmic Solution VIGAMOX®
Dosing Regimen	BID for 3 days	Moxifloxacin AF: BID for 3 days (Vehicle dose at mid-day) VIGAMOX®: TID for 3 days
Patient Population	Adults and children (≥1 month of age) with bacterial conjunctivitis	
Patient Numbers (Planned)	Approx. 600 patients to yield a minimum of 300 bacterial pathogen positive patients (150 per study arm)	Approx. 675 patients to yield a minimum of 370 bacterial pathogen positive patients (185 per study arm)
Primary Efficacy	**Clinical cure** (sum of scores for bulbar conjunctival injection and conjunctival discharge/exudate=0) and **microbiological success** (eradication of pre-therapy pathogens) at the TOC[a] visit.	
Secondary Efficacy	Eight individual signs and symptoms of bacterial conjunctivitis: bulbar conjunctival injection, conjunctival discharge/exudate, lid erythema, lid swelling, palpebral conjunctiva, foreign body sensation, tearing, photophobia.	
Safety Variables	Visual acuity, cornea and iris/anterior chamber, dilated fundus exam, adverse events	
Study Visits	Day 1 (Baseline/Screening); Day 3; Day 4 (EOT[b]: 12-48 hrs after last dose) Day 7 (TOC: 60-96 hrs after last dose)	
Primary Efficacy Data Set	Modified Intent-to-Treat (MITT)[c] Microbiological Intent-to-Treat (MBITT)[c]	Modified Per Protocol (MPP)

[a] Test-of-Cure; [b] End-of-Therapy; [c] The MITT and MBITT data sets differed by a total of 3 patients, 1 randomized to Moxifloxacin AF Ophthalmic Solution and 2 randomized to Vehicle.
Source: This submission, Table 2.3.P.2-1

The primary efficacy data set employed in Study C-04-38 was the Microbiological Intent-to-Treat

(MBITT) data set, defined as all subjects who were pathogen-positive at the screen visit, received at least one dose of study medication, and had at least one on-therapy visit. The primary efficacy set employed in Study C-04-40 was the Modified Per Protocol (MPP) data set, defined as all subjects who met the criteria stated above for the MBITT data set and who met pre-randomization inclusion/exclusion criteria, who had no major protocol violations, and who had both baseline and test of cure (exit) data collected. The protocols defined six data sets, described in Table 21.

Table 21: Data Set Definitions

Analysis Data Set	Patient-Level Evaluability Criteria					
	Receive Drug	Pathogen Positive at Day 1	At Least One On-Therapy Visit	Meet Pre-Randomization Inclusion/ Exclusion Criteria	No Major Protocol Violations	Baseline and Test-of-Cure/ Exit Data
Safety	✓					
ITT[1]	✓		✓			
MBITT[a]	✓	✓	✓			
MITT[a]	✓	✓	✓	✓		
PP[b]	✓		✓	✓	✓	✓
MPP[b]	✓	✓	✓	✓	✓	✓

✓ = Criterion must be met to be evaluable.
[a]Patients with no on-therapy data were included as treatment failures. Include imputed values for all missing data including those for patients who were early discontinuations.
[b]Patients in the ITT and MBITT data sets who discontinued early due to treatment failure were included in these per protocol analyses as treatment failures with patient-level outcomes assigned as failure (note that this was the only data imputation performed).
ITT = Intent-to-Treat; MBITT = Microbiological Intent-to-Treat; MITT = Modified Intent-to-Treat;
PP = Per Protocol; MPP = Modified Per Protocol
Source: This submission, Table 2.3.P.2-3

The hierarchy for defining the study eye is summarized in Table 22.

Table 22: Study Eye Definition

Hierarchical Order for Defining Study Eye	Affected[a] Eye(s)	Pathogen Positive Eye(s)	Study Eye Definition
1	Both	Both	The evaluable eye with the higher score for the cardinal ocular signs[b] at the Day 1 visit
2	Both	One	The pathogen positive eye
3	Both	Neither	The evaluable eye with the higher score for the cardinal ocular signs[b] at the Day 1 visit
4	One	One	The affected eye
5	One	Neither	The affected eye

[a]Affected eye(s) met the pre-therapy inclusion criteria.
[b]If both eyes were rated equally for the two cardinal ocular signs, the right eye was defined as the study eye.
Source: This submission, Table 2.3.P.2-3

Commercial laboratories were contracted by the Applicant to provide clinical microbiology support. For Study C-04-38 (b) (4) was the contract microbiology laboratory. For Study C-04-40, (b) (4)) was the contract microbiology laboratory. The contract laboratories provided an Investigator Laboratory Manual with instructions for specimen collection, as well as supplies for collection and shipping, to each investigator. The Laboratory Manuals (b) (4): C-04-38 Laboratory Investigator's Manual, and (b) (4): C-04-40 Laboratory Investigator's Manual) were not included in the Microbiology Reports. The contract laboratories were responsible for specimen processing, identification of microorganisms, susceptibility testing, shipping all recovered isolates to the Applicant for long-term storage, and reporting results to the Applicant.

Specimens were collected using two sterile disposable "mini-tip" Dacron swabs, one for bacterial culture and the other for adenovirus and Chlamydia culture. The swab for bacterial culture was shipped in an anaerobic/aerobic culture transport system. The swab for chlamydial and viral culture was shipped in a dry sheath. Swabs for bacterial cultured were plated to appropriate media for growth of aerobic and anaerobic microorganisms. Specimen Gram stains were not performed. Swabs for viral/chlamydial culture were tested using the Qiagen QIAmp DNA Mini Kit for amplification and BioSynthesis Fastype™ kits for identification of adenovirus and/or *Chlamydia trachomatis*. Bacteria were identified using API® test strips (bioMerieux) and/or VITEK® (bioMerieux)(C-04-38 only). Susceptibility testing was performed using the Sensititre® Microbial System (Trek Diagnostics), using panels designed by the Applicant. A list of the tested antimicrobials is presented in Table 23. No specific information concerning quality control procedures used in conjunction with any of the tests described above, was provided in the study reports (Report TDOC-0008133 states that "appropriate quality control measures were performed". Persistent pathogens, microorganisms present at Test of Cure visit that were present at the Baseline Visit (pre-therapy), were identified by automated ribotyping, using a Qualicon RiboPrinter. Isolates with identical ribopatterns were considered to be the same infecting strain.

Table 23: Antibiotics for Susceptibility Testing

Antibiotic Class	Antibiotic	Range of Antibiotic Concentrations in Alcon Microtiter Broth Dilution Panels (µg/ml)
Fluoroquinolones	Moxifloxacin (Broth Dilution)	0.004 - 8
	Ciprofloxacin	0.002 - 64
	Ofloxacin	0.008 - 64
Aminoglycosides	Tobramycin	0.015 - 256
	Gentamicin	0.015 - 128
	Neomycin	0.015 - 64
B-lactams	Ampicillin	0.008 - 256
	Ampicillin:Sulbactam	0.12 - 64
	Amoxicillin	0.06 - 128
	Cefazolin	0.06 - 256
	Ceftazidime	0.06 - 256
	Oxacillin	0.03 - 64
	Penicillin	0.015 - 256
	Piperacillin	0.012 - 128
Macrolides	Erythromycin	0.016 - 256
Other Antibiotics	Clindamycin	0.015 - 256
	Polymyxin B	0.06 - 64
	Sulfamethaxazole	0.03 - 512
	Tetracycline	0.03 - 128
	Trimethoprim	0.002 - 256

Source: This submission; Report TDOC-0008133, Table 3.3.2.4.01
Note: Also tested in Study C-0438: Moxifloxacin (Agar Dilution), 0.004-8 mcg/ml and ceftriaxone (anaerobes only), 0.12-0.5 mcg/ml

The Applicant provided no threshold criteria for determining the pathologic significance of isolated bacteria from eye cultures. No such criteria were included in the protocols or Microbiology Reports for C-04-38 (TDOC-0008133) or C-04-40 (TDOC-00008134). All bacteria recovered from collection swabs were presumably reported as "pathogens", regardless of species identification and quantity in culture.

All isolates were shipped to the Applicant for cryopreservation and long term storage.

STUDY C-04-38

Study C-04-38 was performed in the U.S., with patients enrolled from November 3, 2005 through May 17, 2007. A total of 661 subjects were evaluable in the intent-to-treat (ITT) analyses, 345 in the microbiological intent-to-treat (MBITT) analyses, 342 in the modified intent-to-treat (MITT) analyses, 662 in the per protocol (PP) analyses, and 328 in the modified per protocol (MPP) analyses. Demographics were similar in the two arms, with the majority of subjects between 2 and 11 years of age.

The most frequently isolated bacteria from subjects seen in Study C-04-38 were *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Propionibacterium acnes*, *Staphylococcus epidermidis*, and *S. aureus*. No *Chlamydia trachomatis* was identified in subjects seen in this study. Adenovirus was identified in seven subjects (three in eyes identified as "study eyes").

Microbiological and clinical cure rates at the Day 7 Visit are summarized in Tables 24 and 25, respectively. Early clinical cure (Day 4) rates are summarized in Table 26. In the Moxifloxacin AF treatment group (MPP population), 82.7% (115 of 139) of subjects were identified as microbiological successes, with complete eradication of all pre-therapy pathogens. In the vehicle group, 67.7% (90 of 133) of subjects were classified as microbiological success) Of the clinical failures in this group, 17 of 24 had persisting pathogens. No increased resistance was noted in these isolates (Table 27).

Eradication rates (MPP dataset) for the principle bacterial species associated with bacterial conjunctivitis that were treated in the Moxifloxacin AF group were:

- 89% (25 of 28) *Streptococcus pneumoniae*
- 100% (20 of 20) *Staphylococcus epidermidis*
- 100% (7 of 7) *S. aureus*
- 71% (32 of 45) *Haemophilus influenzae*
- 96% (24 of 25) *Propionibacterium acnes*

Table 24: Microbiological Success Rate at the Day 7 (TOC) Visit

	Treatment								
	Moxi AF				Vehicle				
	Microbiological Outcome				Microbiological Outcome				
	Success		Failure		Success		Failure		
Data Set	N	%	N	%	N	%	N	%	p-value[a]
MBITT	150	84.3	28	15.7	110	65.9	57	34.1	<.0001
MITT	149	84.2	28	15.8	109	66.1	56	33.9	0.0001
MPP	115	82.7	24	17.3	90	67.7	43	32.3	0.0039

[a]Chi-square test of independence (or Fisher's Exact test if N<5)

Source: Table 2.7.3.2.-4; this submission

Table 25: Clinical Cure at the Day 7 (TOC) Visit

	Treatment								
	Moxi AF				Vehicle				
	Clinical Cure at TOC				Clinical Cure at TOC				
	Yes		No		Yes		No		
Data Set	N	%	N	%	N	%	N	%	p-value[a]
ITT	245	74.0	86	26.0	217	65.8	113	34.2	0.0206
MBITT	129	72.5	49	27.5	113	67.7	54	32.3	0.3295
MITT	128	72.3	49	27.7	111	67.3	54	32.7	0.3097
PP	199	75.4	65	24.6	170	65.9	88	34.1	0.0173
MPP	105	75.0	35	25.0	88	66.2	45	33.8	0.1089

[a]Chi-square test of independence (or Fisher's Exact test if N<5)

Source: Table 2.7.3.2.-5; this submission

Table 26: Clinical Cure Rate at the Day 4 (EOT) Visit

	Treatment								
	Moxi AF				Vehicle				
	Clinical Cure				Clinical Cure				
	Yes		No		Yes		No		
Data Set	N	%	N	%	N	%	N	%	p-value[a]
ITT	196	59.2	135	40.8	142	43.0	188	57.0	<.0001
MBITT	104	58.4	74	41.6	78	46.7	89	53.3	0.0293
MITT	103	58.2	74	41.8	77	46.7	88	53.3	0.0329
PP	146	59.1	101	40.9	99	41.9	137	58.1	0.0002
MPP	80	60.6	52	39.4	54	44.3	68	55.7	0.0091

[a]Chi-square test of independence (or Fisher's Exact test if N<5)

Source: Table 2.7.3.2.-5; this submission

Table 27: Moxi AF Treatment Failures Due to Persistence (MPP – Moxifloxacin AF)

Inv	Pt	Organisms Isolated at Pre-therapy	MOX[a] MIC	Days On Therapy	Failure[b] Day	Organisms Isolated at Time of Failure	MOX[a] MIC
2475	1401	*Haemophilus influenzae*	0.015	3	6	*Haemophilus influenzae*	0.015
		Propionibacterium acnes	0.19				
		Staphylococcus aureus	0.03				
2475	1424	*Haemophilus* species	0.03	3	6	*Haemophilus* species	0.03
2833	202	*Haemophilus influenzae*	0.03	3	6	*Haemophilus influenzae*	0.03
		Moraxella catarrhalis	0.03				
2833	204	*Haemophilus influenzae*	0.06	3	7	*Haemophilus influenzae*	0.06
2833	222	*Haemophilus influenzae*	0.015	3	7	*Haemophilus influenzae*	0.03
		Staphylococcus epidermidis	0.12				
2833	226	*Haemophilus influenzae*	0.008	3	6	*Haemophilus influenzae*	0.008
3475	803	*Haemophilus influenzae*	0.015	3	7	*Haemophilus influenzae*	0.015
		Haemophilus influenzae	0.03			*Streptococcus sanguis*	0.12
		Staphylococcus epidermidis	0.06			*Streptococcus* species	0.12
		Streptococcus pneumoniae	0.12				
3545	303	*Streptococcus pneumoniae*	0.12	3	6	*Streptococcus pneumoniae*	0.12
3545	319	*Haemophilus influenzae*	0.015	3	6	*Haemophilus influenzae*	0.03
		Chryseobacterium indologenes	0.06				
		Streptococcus species	0.06				
4042	1614	*Propionibacterium acnes*	0.094	3	6	*Propionibacterium acnes*	0.19
4055	2307	*Haemophilus influenzae*	0.015	3	8	*Haemophilus influenzae*	0.015
4576	2210	*Streptococcus pneumoniae*	0.015	3	6	*Streptococcus pneumoniae*	0.015
4576	2216	*Haemophilus influenzae*	0.015	3	6	*Haemophilus influenzae*	0.015
4576	2218	*Haemophilus influenzae*	0.03	3	5	*Haemophilus influenzae*	0.03
4580	719	*Haemophilus influenzae*	0.03	3	7	*Haemophilus influenzae*	0.015
		Streptococcus mitis	0.12			*Rothia dentocariosa*	0.12
						Streptococcus pneumoniae	0.12
4795	3018	*Haemophilus influenzae*	0.032	3	7	No specimen collected	
		Streptococcus pneumoniae	0.12				
5006	4001	*Haemophilus influenzae*	0.03	3	7	*Haemophilus influenzae*	0.015

Inv = Investigator
Pt = Patient
[a]Moxifloxacin MIC
[b]Treatment failure day is the day this micro failure occurred on (exam date - baseline date + 1).
Patients could have multiple organisms at pre-therapy and/or exit.

STUDY C-04-40

Study C-04-40 was performed in India, with patients enrolled from May 2, 2006 through December 26, 2006. A total of 695 subjects were evaluable in the intent-to-treat (ITT) analyses, 382 in the microbiological intent-to-treat (MBITT) analyses, 378 in the modified intent-to-treat (MITT) analyses, and 246 in the modified per protocol (MPP) analyses. A significant majority of subjects enrolled in Study C-04-40 were 18 years of age or older (96 subjects less than 18 years of age, 599 subjects aged 18 years and older).

The most frequently isolated bacteria from subjects seen in Study C-04-40 were *Staphylococcus epidermidis*, *S. haemolyticus*, *S. aureus*, and *Micrococcus luteus*. Fifteen cases of Chlamydia trachomatis infection were included in the MPP dataset (5 in the Moxifloxacin AF arm, 10 in the Vigamox arm). Report TDOC-0008134 (Study C-04-40) states that adenovirus was recovered, but the number of isolates was not provided. No isolates of either Streptococcus pneumoniae or Haemophilus influenzae were recovered in Study C-04-40.

The microbiological success rate was 92.6% in the Moxifloxacin AF treatment group, and 92.9% in the VIGAMOX treatment group. Microbiological and clinical cure rates at the Day 7 Visit are summarized in Tables 28 and 29, respectively. Early clinical cure (Day 4) rates are summarized

in Table 30. In the Moxifloxacin AF treatment group (MPP population), 92.6% (112 of 121) of subjects were identified as microbiological successes, with complete eradication of all pre-therapy pathogens. In the Vigamox group, 92.0% (115 of 125) of subjects were classified as microbiological success. Of the clinical failures, no subjects were identified with persisting pathogens.

Eradication rates (MPP dataset) for the principle bacteria associated with bacterial conjunctivitis that were treated in the Moxifloxacin AF group were:

- 100% (33 of 33) *Staphylococcus epidermidis*
- 100% (12 of 12) *S. aureus*
- 100% (6 of 6) *S. haemolyticus*
- 100% (3 of 3) *Chlamydia trachomatis*

Table 28: Microbiological Success Rate at the Day 7 (TOC) Visit

	Treatment											
	Moxi AF				VIGAMOX®							
	Microbiological Outcome				Microbiological Outcome							
	Success		Failure		Success		Failure					
Data Set	N	%	N	%	N	%	N	%	p-value[a]	Delta	LCL[b]	UCL[b]
MBITT	165	87.3	24	12.7	173	89.6	20	10.4	0.4746	-2.3	-8.7406	4.0691
MITT	163	87.2	24	12.8	171	89.5	20	10.5	0.4739	-2.3	-8.8312	4.1052
MPP	112	92.6	9	7.4	115	92.0	10	8.0	0.8689	0.6	-6.1072	7.2311

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
[b]95% Conf. Limits for Moxi AF-VIGAMOX®
Source: Table 2.7.3.2.-8; this submission

Table 29: Clinical Cure at the Day 7 (TOC) Visit

	Treatment											
	Moxi AF				VIGAMOX®							
	Clinical Cure				Clinical Cure							
	Yes		No		Yes		No					
Data Set	N	%	N	%	N	%	N	%	p-value[a]	Delta	LCL[b]	UCL[b]
ITT	279	80.6	67	19.4	289	82.8	60	17.2	0.4587	-2.2	-7.9174	3.5730
MBITT	152	80.4	37	19.6	163	84.5	30	15.5	0.3001	-4.1	-11.6571	3.5918
MITT	150	80.2	37	19.8	161	84.3	30	15.7	0.2991	-4.1	-11.7757	3.6171
PP	197	82.1	43	17.9	197	86.0	32	14.0	0.2442	-3.9	-10.5540	2.6682
MPP	103	84.4	19	15.6	108	85.7	18	14.3	0.7759	-1.3	-10.1614	7.5852

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
[b]95% Conf. Limits for Moxi AF-VIGAMOX®
Source: Table 2.7.3.2.-9; this submission

Table 30: Clinical Cure at the Day 4 (EOT) Visit

	Treatment											
	Moxi AF Clinical Cure				VIGAMOX® Clinical Cure							
	Yes		No		Yes		No					
Data Set	N	%	N	%	N	%	N	%	p-value[a]	Delta	LCL[b]	UCL[b]
ITT	199	57.5	147	42.5	214	61.3	135	38.7	0.3072	-3.8	-11.1001	3.4929
MBITT	109	57.7	80	42.3	125	64.8	68	35.2	0.1547	-7.1	-16.8437	2.6539
MITT	108	57.8	79	42.2	123	64.4	68	35.6	0.1852	-6.6	-16.4539	3.1661
PP	136	58.9	95	41.1	145	64.7	79	35.3	0.1987	-5.8	-14.7694	3.0540
MPP	73	62.4	44	37.6	80	65.0	43	35.0	0.6698	-2.6	-14.8154	9.5204

[a]Chi-square test of independence (or Fisher's Exact test if N<5)
[b]95% Conf. Limits for Moxi AF-VIGAMOX®
Source: Table 2.7.3.2.-10; this submission

SUMMARY OF CLINICAL STUDIES

Data from the two Phase 3 clinical trials submitted in support of the Application suggest that Moxifloxacin AF Ophthalmic Solution, 0.5% is effective in eradicating the principle pathogens associated with bacterial conjunctivitis. With the exception of *Haemophilus influenzae* (eradiation rate = 71% in patients treated with Moxifloxacin AF), eradication rates for all principle pathogens commonly associated with bacterial conjunctivitis were approximately 90% or higher. In cases where *Staphylococcus epidermidis* was isolated (an organism with potential non-susceptibility to fourth-generation fluoroquinolones), 100% of the pathogens were eradicated. Increased resistance to moxifloxacin was not noted in isolates defined as persistent pathogens in Study 04-38 (no persistent pathogens were identified in Study C-04-40). Summaries of eradication rates, per pathogen, are presented in Tables 31 and 32.

Table 31: Eradication Rate of Pre-therapy Pathogens by Moxifloxacin AF Ophthalmic Solution

Clinical Study C-04-38 and C-04-40	MOXI AF Treatment		
Bacterial Species	E	P	%
Staphylococcus epidermidis	53	0	100
Haemophilus influenzae	32	13	71
Streptococcus pneumoniae	26	3	90
Propionibacterium acnes	24	1	96
Staphylococcus aureus	19	0	100
Staphylococcus arlettae	8	0	100
Viridans Streptococcus	7	0	100
Staphylococcus haemolyticus	6	0	100
Staphylococcus hominis	6	0	100
Staphylococcus capitis	6	0	100
Staphylococcus warneri	4	0	100
Klebsiella pneumoniae	4	0	100
Enterococcus faecalis	4	0	100
Chlamydia trachomatis	3	0	100
Micrococus luteus	3	0	100
Staphylococcus saprophyticus	3	0	100
Staphylococcus scuri	3	0	100
Bacillus cereus	3	0	100
Corynebacterium propinquum	3	0	100
Aerococcus viridans	3	0	100
Staphylococcus cohnii	3	0	100
Corynebacterium species	2	0	100
Microbacterium species	2	0	100
Streptococcus mitis	2	0	100
Pseudomonas aeruginosa	2	0	100
Citrobacter koseri	2	0	100
Enterobacter hormaechei	2	0	100
Bacillus subtilis	2	0	100
Streptococcus parasanguinis	2	0	100
Streptococcus peroris	2	0	100
Pantoea species	1	0	100
Staphylococcus lugdunensis	1	0	100
Bacillus species.	1	0	100
Actinomyces naeslundii	1	0	100
Bacillus circulans	1	0	100
Bacillus simplex	1	0	100
Clostridium bifermentans	1	0	100
Corynebacterium argentoratense	1	0	100
Corynebacterium macginleyi	1	0	100
Kocuria kristinae	1	0	100
Lactococcus lactis	1	0	100
Staphylococcus pasteuri	1	0	100
Streptococcus oralis	1	0	100
Streptococcus thermophilus	1	0	100
Serratia liquefaciens	1	0	100
Acentobacter ursingii	1	0	100
Moraxella lacunata	1	0	100
Neisseria meningitidis	1	0	100
Bacillus pumilus	1	0	100
Brevibacterium casei	1	0	100
Corynebacterium accolens	1	0	100
Paenibacillus species	1	0	100
Staphylococcus caprae	1	0	100
Escherichia coli	1	0	100
Serratia species	1	0	100
Acinetobacter baumannii	1	0	100
Acinetobacter schlindleri	1	0	100
Pseudomonas stutzeri	1	0	100

E=number of isolates eradicated in successfully treated patients
P=number of isolates persisting in failed patients
%= Eradication Rate

Table 32: Eradication Rates for Conjunctivitis Isolates Treated with Moxifloxacin 0.5%

	All Treatments with Moxifloxacin 0.5%[a]			Moxifloxacin AF Treatments[b]			VIGAMOX® Treatments[c]		
Aerobic Gram-Positives	**E**	**P**	**%**	**E**	**P**	**%**	**E**	**P**	**%**
Streptococcus pneumoniae	48	7	87	26	3	90	22	4	85
Streptococcus viridans group	26	0	100	7	0	100	19	0	100
Streptococcus mitis	8	0	100	2	0	100	6	0	100
Staphylococcus epidermidis	166	2	99	53	0	100	113	2	98
Staphylococcus aureus	66	0	100	19	0	100	47	0	100
Staphylococcus haemolyticus	36	3	92	6	0	100	30	3	91
Staphylococcus hominis	16	0	100	6	0	100	10	0	100
Staphylococcus warneri	11	0	100	4	0	100	6	0	100
Staphylococcus capitis	10	0	100	6	0	100	4	0	100
Staphylococcus saprophyticus	7	0	100	3	0	100	4	0	100
Staphylococcus scuri	6	0	100	3	0	100	3	0	100
Enterococcus faecalis	7	0	100	4	0	100	3	0	100
Enterococcus gallinarum	6	0	100	0	0	-	6	0	100
Corynebacterium species	14	0	100	8	0	100	6	0	100
Bacillus species	12	0	100	3	0	100	9	0	100
Micrococus luteus	14	0	100	3	0	100	11	0	100
Anaerobes:									
Propionibacterium acnes	24	1	96	24	1	96	0	0	-
Aerobic Gram-Negatives	**E**	**P**	**%**	**E**	**P**	**%**	**E**	**P**	**%**
Haemophilus influenzae	62	22	74	32	13	71	30	9	77
Acinetobacter species	16	0	100	3	0	100	13	0	100
Klebsiella pneumoniae	10	0	100	4	0	100	6	0	100
Serratia species	9	0	100	2	0	100	7	0	100
Enterobacter hormaechei	8	0	100	2	0	100	6	0	100
Other:									
Chlamydia trachomatis	34	2	94	3	0	100	31	2	94

[a] Total # of isolates from both (b) Moxi AF Treatment: C-04-38 and C-04-40 and (c)VIGAMOX® Treatment: C-00-55, C-00-46 C-01-34, C-01-66, and C-04-40.
[b] Includes isolates from only Moxi AF treated patients in C-04-38 and C-04-40
[c] Includes isolates from VIGAMOX® Treatment: Studies C-00-55, C-00-46, C-01-34, C-01-66, and C-04-40
E=number of isolates eradicated in successfully treated patients
P=number of isolates persisting in failed patients
%= Eradication Rate

The two clinical trials differed significantly in both the demographics of the study populations and in the bacteria isolated from the subjects in these groups. Notably, no isolates of either *Haemophilus influenzae* or *Streptococcus pneumoniae* were recovered in Study C-04-40, despite the fact that these species are considered to be among the most common causes of bacterial conjunctivitis [Mandell 2005]. Similarly, no isolates of *Chlamydia trachomatis* were recovered in Study C-04-38. These anomalies may be partially explained by the disparity in demographic groups represented in the two trials (Study C-04-38 enrolled primarily subjects ≤ 11 years of age, while Study C-04-40 enrolled primarily patients ≥ 18 years of age) and their geographic location (Study C-04-38 was performed in the U.S., Study C-04-40 was performed in India).

6 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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F. Marsik, Ph.D.
Micro/TL/HFD520
7Jul 09 FIN FJM

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22428	ORIG 1	ALCON PHARMACEUTICALS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

KERRY SNOW
08/23/2009

FREDERIC J MARSIK
08/24/2009

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 22-428: Moxifloxacin Alternative Formulation Ophthalmic Solution for Bacterial Conjunctivitis
Reviewer: Kerry Snow Date Review completed: 14 January 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?	✓		
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?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant submitted *in vitro* 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?	✓		
5	Has the applicant submitted 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?	✓		
6	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	✓		

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/s/

Kerry Snow
1/26/2009 04:45:58 PM
MICROBIOLOGIST

Frederic Marsik
1/27/2009 06:32:02 AM
MICROBIOLOGIST

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-428 **Applicant: Alcon Pharmaceuticals Ltd.** **Letter Date: 12 DEC 2008**

Drug Name: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution **NDA Type: 505(b)(1)** **Stamp Date: 15 DEC 2008**

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

	Content Parameter	Yes	No	Comments
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?	**X**		Submitted in CTD format as bound paper copies.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	**X**		Module 3, Volume 1.3, Section 3.2.P.3.1-3.4
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	**X**		
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?		**X**	
5	Has the applicant submitted (b) (4) effectiveness studies (if applicable) and container-closure integrity studies?	**X**		Module 3, Vol. 1.3, Section 3.2.P.2.5 and Tab TDOC 0006409
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	**X**		Module 3 Vol. 1.4, Section 3.2.P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	**X**		Module 3, Vol. 1.3, Section 3.2.P.2.5, Tabs 4-6
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	N/A
9	Is this NDA fileable? If not, then describe why.	**X**		

Additional Comments: The applicant submitted the bacterial endotoxin acceptance criterion for release as NMT (b) (4) (equivalent to Less Than (b) (4) The criterion should be stated as EU/ml, not EU/dose. 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.

Robert J. Mello, Ph.D., Review Microbiologist Date

Bryan S. Riley, Ph.D., Senior Microbiology Reviewer Date

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/s/

Robert Mello
1/23/2009 01:51:52 PM
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Submission is fileable

Bryan Riley
1/23/2009 01:55:22 PM
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I concur.