

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22428Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	N
Application Number(s)	NDA 22-428
Priority or Standard	Standard
Submit Date(s)	May 20, 2010
Received Date(s)	May 21, 2010
PDUFA Goal Date	November 19, 2010
Division / Office	DAIOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	November 19, 2010
Established Name	moxifloxacin hydrochloride ophthalmic solution 0.5% as base
(Proposed) Trade Name	Moxeza
Therapeutic Class	quinolone
Applicant	Alcon Research Ltd.
Formulation(s)	Ophthalmic solution
Dosing Regimen	One (1) drop in the affected eye(s) twice a day
Indication(s)	Bacterial conjunctivitis
Intended Population(s)	Patients ages 1 year and older with bacterial conjunctivitis

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	5
1.1	Recommendation on Regulatory Action	5
1.2	Risk Benefit Assessment	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	5
1.4	Recommendations for Postmarket Requirements and Commitments	5
2	INTRODUCTION AND REGULATORY BACKGROUND.....	5
2.1	Product Information.....	6
2.2	Tables of Currently Available Treatments for Proposed Indications	6
2.3	Availability of Proposed Active Ingredient in the United States	6
2.4	Important Safety Issues With Consideration to Related Drugs.....	6
2.5	Summary of Presubmission Regulatory Activity Related to Submission	6
2.6	Other Relevant Background Information	7
3	ETHICS AND GOOD CLINICAL PRACTICES	7
3.1	Submission Quality and Integrity	7
3.2	Compliance with Good Clinical Practices.....	7
3.3	Financial Disclosures.....	7
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	8
4.1	Chemistry Manufacturing and Controls	8
4.2	Clinical Microbiology.....	9
4.3	Preclinical Pharmacology/Toxicology	9
4.4	Clinical Pharmacology	9
4.4.1	Mechanism of Action	9
4.4.2	Pharmacodynamics.....	9
4.4.3	Pharmacokinetics.....	10
5	SOURCES OF CLINICAL DATA.....	10
5.1	Tables of Studies/Clinical Trials	10
5.2	Review Strategy.....	10
5.3	Discussion of Individual Studies/Clinical Trials	10
6	REVIEW OF EFFICACY	20
	Efficacy Summary	20
6.1	Indication.....	20
6.1.1	Methods.....	21
6.1.2	Demographics.....	21
6.1.3	Subject Disposition.....	22
6.1.4	Analysis of Primary Endpoint(s).....	23
6.1.5	Analysis of Secondary Endpoints(s)	24

6.1.6	Other Endpoints.....	25
6.1.7	Subpopulations	25
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	26
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	26
6.1.10	Additional Efficacy Issues/Analyses.....	26
7	REVIEW OF SAFETY	27
	Safety Summary.....	27
7.1	Methods	27
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	28
7.1.2	Categorization of Adverse Events.....	29
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	29
7.2	Adequacy of Safety Assessments	29
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	29
7.2.2	Explorations for Dose Response	30
7.2.3	Special Animal and/or In Vitro Testing	30
7.2.4	Routine Clinical Testing.....	30
7.2.5	Metabolic, Clearance, and Interaction Workup.....	30
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	30
7.3	Major Safety Results	30
7.3.1	Deaths.....	30
7.3.2	Nonfatal Serious Adverse Events.....	30
7.3.3	Dropouts and/or Discontinuations.....	31
7.3.4	Significant Adverse Events	32
7.3.5	Submission Specific Primary Safety Concerns	32
7.4	Supportive Safety Results.....	32
7.4.1	Common Adverse Events.....	32
7.4.2	Laboratory Findings	34
7.4.3	Vital Signs	34
7.4.4	Electrocardiograms (ECGs)	35
7.4.5	Special Safety Studies/Clinical Trials	35
7.4.6	Immunogenicity.....	35
7.5	Other Safety Explorations	35
7.5.1	Dose Dependency for Adverse Events.....	35
7.5.2	Time Dependency for Adverse Events.....	35
7.5.3	Drug-Demographic Interactions.....	35
7.5.4	Drug-Disease Interactions	35
7.5.5	Drug-Drug Interactions	35
7.6	Additional Safety Evaluations	36
7.6.1	Human Carcinogenicity.....	36
7.6.2	Human Reproduction and Pregnancy Data	36
7.6.3	Pediatrics and Assessment of Effects on Growth.....	36

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	36
7.7	Additional Submissions / Safety Issues.....	36
8	POSTMARKET EXPERIENCE.....	36
9	APPENDICES.....	38
9.1	Literature Review/References	38
9.2	Labeling Recommendations	38
9.3	Advisory Committee Meeting	38

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-428 be approved with the labeling revisions found in this review.

1.2 Risk Benefit Assessment

The data contained in the clinical trial submitted in this re-submission (Study C-07-40) along with the Agency's prior finding of efficacy of moxifloxacin hydrochloride ophthalmic solution 0.5% in NDA 21-598 (Vigamox) establish the efficacy of moxifloxacin AF in the treatment of bacterial conjunctivitis. Study C-07-40 met its pre-specified primary endpoint of clinical cure at Day 4. Microbiological success was also demonstrated at Day 4.

There are no new safety concerns raised in this NDA submission concerning the use of moxifloxacin for the treatment of bacterial conjunctivitis. The adverse events reported during the phase 3 studies were similar to those listed in the package insert of the currently marketed fluoroquinolone ophthalmic solutions. No clinically significant differences were found between moxifloxacin AF and the active control Vigamox in the frequency or type of adverse events.

The benefit of moxifloxacin in the treatment of bacterial conjunctivitis has been demonstrated in this NDA application. The risk for using this drug is minimal and is consistent with the currently marketed Vigamox.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarket clinical study requirements and commitments.

2 Introduction and Regulatory Background

Moxifloxacin is a fourth generation quinolone that was originally developed and approved for the treatment of various systemic bacterial infections. Alcon developed a topical ophthalmic formulation of moxifloxacin marketed as Vigamox for the treatment of bacterial conjunctivitis. The approved dosage and administration for Vigamox is one drop in the affected eye 3 times a

day for 7 days. The current application is for an alternate formulation of moxifloxacin for the treatment of bacterial conjunctivitis. The alternate formulation contains a xanthan gum-^{(b) (4)} ^{(b) (4)} which is expected by Alcon to ^{(b) (4)}. The objective of this change is to maintain the same efficacy as Vigamox with only twice a day dosing.

2.1 Product Information

Established Name: moxifloxacin hydrochloride ophthalmic solution 0.5%
Proposed Trade Name: Moxeza
Chemical Class: new formulation
Pharmacological Class: quinolone
Indication: treatment of bacterial conjunctivitis

Dosing Regimen: One drop in the affected eye(s) two times a day for seven days
Age Groups: adults and children over the age of four months

2.2 Tables of Currently Available Treatments for Proposed Indications

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

2.3 Availability of Proposed Active Ingredient in the United States

Moxifloxacin hydrochloride was approved in Alcon's NDA 21-598 for Vigamox and is currently being marketed in the United States. Moxifloxacin hydrochloride is manufactured by Bayer AG in Wuppertal, Germany.

2.4 Important Safety Issues With Consideration to Related Drugs

Ophthalmic anti-infectives are generally well tolerated and effective for bacterial conjunctivitis. There are no specific issues which warrant special attention.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Alcon's proposed phase 3 development program for moxifloxacin AF ophthalmic solution was discussed with the Agency in a pre-IND/end of phase 2 meeting on March 3, 2005. Alcon subsequently submitted Special Protocol Assessment requests for study C-04-38 and C-04-40, to which the Agency responded with comments on June 22, 2005. Comments on both studies were provided to the applicant. A pre-NDA meeting package containing a summary of efficacy

results from these studies was submitted to the Agency and comments were discussed at the pre-NDA meeting on April 8, 2008.

2.6 Other Relevant Background Information

The original NDA submission was submitted on December 12, 2008. FDA issued a complete response letter dated October 7, 2009, stating that there was a lack of substantial evidence to demonstrate efficacy in the submission. The Agency recommended that any resubmission contain the results from at least one additional vehicle-controlled clinical trial.

Moxifloxacin AF is not marketed in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

The clinical studies included in this application conformed with Good Clinical Practices

3.3 Financial Disclosures

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for moxifloxacin AF ophthalmic solution. There are three investigators who participated in the phase (b) (6) who have disclosed financial ties to the sponsor.

Investigators with financial Interests or Arrangements

Clinical Study	Investigators
(b) (6)	(b) (6)

Reviewer's Comments:

A review of these arrangements does not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Moxifloxacin Alternative Formulation Ophthalmic solution, 0.5% is a sterile, stable, self-preserved ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride. The product was developed using the same active ingredient and for the same indication (topical treatment of bacterial conjunctivitis) as Vigamox. The modified formulation contains a xanthan gum (b) (4)

Composition of Moxifloxacin AF Ophthalmic Solution

Component	Percent w/v	Purpose
Moxifloxacin hydrochloride	0.545	Active
Xanthan gum	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	(b) (4)
Boric acid	(b) (4)	(b) (4)
Sorbitol	(b) (4)	(b) (4)
Tyloxapol	(b) (4)	(b) (4)
Hydrochloric acid and/or sodium hydroxide	Adjust pH to 7.4	pH adjuster
Purified water	(b) (4)	(b) (4)

Comparison of Compositions of Moxifloxacin AF and Vigamox

Component	% Composition	
	Moxifloxacin AF	Vigamox
Moxifloxacin hydrochloride	0.545	same
Xanthan gum	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	(b) (4)
Boric acid	(b) (4)	(b) (4)
Sorbitol	(b) (4)	(b) (4)
Tyloxapol	(b) (4)	(b) (4)
Hydrochloric acid and/or sodium hydroxide	Adjust pH to 7.4	Adjust to pH 6.8
Purified water	(b) (4)	(b) (4)

The formulation of Moxifloxacin AF that was used in the clinical studies are the same as the one intended for marketing.

4.2 Clinical Microbiology

See section 6.1.10.

4.3 Preclinical Pharmacology/Toxicology

Ocular PK studies in rabbits showed that the concentration of moxifloxacin in tears fell more rapidly following application of Vigamox than following application of Moxifloxacin AF. Additionally, the levels of moxifloxacin in the aqueous humor of rabbits were higher after application of Moxifloxacin AF compared to Vigamox. Although the clinical significance is not known.

Moxifloxacin AF was well tolerated by rabbits when applied to the eyes several times daily for one month. Neither ocular irritation nor toxicity was observed with the formulation and concentration of active ingredient to be marketed. There were microscopic signs of slight irritation at higher moxifloxacin concentrations >1% (same vehicle as Moxifloxacin AF), but no inflammation.

Moxifloxacin AF appears reasonably safe to use as directed. This product caused neither ocular irritation nor toxicity when applied to rabbit eyes several times daily for one month.

See Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for moxifloxacin was previously submitted and evaluated as part of the Vigamox NDA (NDA 21-598). The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA.

Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

4.4.2 Pharmacodynamics

See Biopharmaceutics review.

4.4.3 Pharmacokinetics

See Biopharmaceutics review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
C-07-40 Safety/ efficacy study	Prospective, multi-center randomized, vehicle- controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution	1 drop BID OU	3 days	1179 (847 culture positive diagnosed eye)
			Vehicle	1 drop BID OU		

5.2 Review Strategy

This re-submission contained one additional safety and efficacy trial to support the approval of moxifloxacin AF for the treatment of bacterial conjunctivitis. Study C-07-40 was a two-arm superiority trial comparing moxifloxacin AF to vehicle.

The original NDA submission contained two safety and efficacy trials to support the approval of moxifloxacin AF for the treatment of bacterial conjunctivitis. Study C-04-38 was a two-arm superiority trial comparing moxifloxacin to vehicle; study C-04-40 was a non-inferiority trial which compared the new formulation to the currently marketed Vigamox. Study C-04-38 failed its pre-specified primary efficacy endpoint of clinical cure at day 7; however, microbiological eradication was demonstrated at this timepoint. Since a non-inferiority margin has not been established for Vigamox, Study C-04-40 was not viewed as a study that could be used to establish the efficacy moxifloxacin AF and was considered supportive evidence.

All three studies were used in the safety analysis.

5.3 Discussion of Individual Studies/Clinical Trials

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Study C-07-40

Title: An Evaluation of the Safety and Efficacy of Moxifloxacin AF Ophthalmic Solution 0.5% for the Treatment of Bacterial Conjunctivitis in the USA

Study Design

This study was a prospective, multi-center (32 sites), double-masked, parallel group, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of topical ocular moxifloxacin AF ophthalmic solution compared to vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. Approximately 1644 patients with a clinical diagnosis of bacterial conjunctivitis were targeted for enrollment to achieve at least 822 (411 on moxifloxacin AF ophthalmic solution and 411 on vehicle) bacterial pathogen positive patients. Enrollment in the study included patients one month of age or older and excluded all considerations of race, occupation, socioeconomic status, or gender.

On Day 1, eligible patients who met all inclusion/exclusion criteria were randomized into one of two treatment groups, moxifloxacin AF ophthalmic solution or vehicle. Both groups were dosed with one drop two times per day. Treatment continued for 3 days with a test-of-cure (clinical) follow-up visit at 12 to 48 hours after the last dose of study medication [Day 4, End of Therapy (EOT)].

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Study Plan

Procedures	Day 1 (Screening/ Baseline) Visit	Day 3 (-1) Visit	Day 4(EOT)/Exit Visit^a Or Early Exit Visit^b
Screen for inclusion/exclusion criteria	X		
Informed Consent/Assent ^c	X		
Urine Pregnancy Test	X ^d		X ^d
General Information; Medical History	X		
Vaccination Information (Patients ≤12 yrs)	X		
Changes in concomitant medication or general health		X	X
Patients or Parent/Guardian Rate Ocular Symptoms	X	X	X
Visual Acuity logMAR	X	X	X
Investigator Rates Ocular Signs	X	X	X
Ocular Examination (Cornea,Iris/Anterior Chamber and Lens)	X	X	X
Collect Ocular Microbiological Specimens	X ^e		X ^e
Fundus Exam ^f	X ^f		X ^f
First Dose of Study Medication (in-office)	X		
Dispense Study Medication	X	X ^h	
Record Adverse Events	X ^g	X	X
Collect Study Medication		X ^h	X
Complete Exit Form			X

Best Available Copy

^a The Day 4 (EOT)/Exit Visit was conducted 12 to 48 hours after the last study dose and was performed by an ophthalmologist sub-investigator at sites where the principal investigator was a non-ophthalmologist.

^b If a patient exited prior to the Day 4 (EOT)/Exit Visit, an Early Exit Visit was conducted that included all Day 4 procedures. This exam was performed within 24 hours of exit by an ophthalmologist Sub-Investigator at sites where the principal investigator was a non-ophthalmologist.

^c Assent collected for patients over 6 and under 18 years of age, if applicable

^d For women of child-bearing potential, UPT done before instillation of drug and at study exit.

^e Specimens were collected prior to the fundus exam.

^f All Day 1 (Screening/Baseline) Visit and Day 4 fundus examinations by Ophthalmologist utilized pupil dilation. All Day 1 (Screening/Baseline) Visit non-ophthalmologist fundus exams were undilated. A red reflex fundus exam was conducted in infants and uncooperative children.

^g After dosing

^h As needed

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Inclusion Criteria

1. One month of age or older, of any race and either sex
2. Diagnosed with bacterial conjunctivitis in 1 or both eyes based upon the following clinical observations:
 - A rating of ≥ 1 for bulbar conjunctival injection and
 - A rating of ≥ 1 for conjunctival discharge/exudate in at least 1 eye (the same eye) at the Day 1 (Screening/Baseline) Visit, and
Note: Rating was on a scale of 0-3 (absent to severe)
 - Must have been experiencing matting, currently or upon waking.
3. Were able to understand and sign an informed consent form that was approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC). If the patient was under 18 years of age, the informed consent must have been understood and signed by the patient's legally authorized representative (parent or guardian). Assent to participate in the study was obtained from patients over 6 and under 18 years of age unless not allowed by local regulation.
4. Agreed to comply with the visit schedule and other requirements of the study. The parent or guardian must have agreed to ensure compliance of patients less than 18 years of age.
5. Women who were not pregnant and not lactating. Women who were post-menopausal or surgically sterilized. All women of childbearing potential (those who were post-menarcheal, pre-menopausal and not surgically sterile) could participate only if they had a negative urine pregnancy test prior to randomization, and if they had agreed to use adequate birth control methods to prevent pregnancy throughout the study. Adequate birth control methods included hormonal, topical, oral, implanted or injected contraceptives; mechanical – spermicide in conjunction with a barrier such as a condom or diaphragm, intrauterine device (IUD); surgical sterilization of partner.

Exclusion Criteria

1. Signs and symptoms of bacterial conjunctivitis for longer than 4 days prior to Day 1 (Screening/Baseline) Visit
2. Abnormal findings in the posterior pole of the retina or any media opacity found in a fundus examination at the Day 1 (Screening/Baseline) Visit
3. Presence of inflammation and/or active structural change in the cornea, iris, anterior chamber or lens at the Day 1 (Screening/Baseline) Visit
4. Presence of corneal opacity or any corneal abnormality at the Day 1 (Screening/Baseline) Visit that would impact the outcome of the study
5. Presence of concomitant viral infection
6. Presence of nasolacrimal duct obstruction at Day 1 (Screening/Baseline) Visit
7. Infants who had suspected or confirmed ophthalmia neonatorum of gonococcal, Chlamydia, herpetic or chemical origin
8. Infants whose birth mothers had any sexually transmitted disease within 1 month prior to delivery
9. Infants who were undergoing treatment for retinopathy of prematurity

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

10. Contact lens wear during the course of the study
11. Patients who had only 1 sighted eye or vision in either eye not correctable to 0.6 logMAR units (20/80) or better (using ETDRS chart). For patients who were too young to use an ETDRS chart, an age appropriate measurement method supplied by the Sponsor in accordance with the American Academy of Pediatrics Eye Examination and Vision Screening in Infants, Children and Young Adults (RE9625) Policy Statement was used. The policy statement stated that formal vision screening should begin at 3 years of age. Visual acuity measurements for children under 3 were done at the discretion of the Investigator. If not conducted, the child had to be able to fixate on and follow a moving object. Visual acuity was measured using the same method for each patient at each visit.
12. Suspected fungal, viral (e.g., Herpes Simplex) or Acanthamoeba infection, based upon clinical observation
13. Use of any preserved topical ocular medications (prescribed or OTC) at the time of entry into the study or during study participation
14. Use of any oral or topical ocular antibacterial agent within the 72 hours prior to Day 1 (Screening/Baseline) Visit or during study participation
15. Use of systemic steroids within 14 days prior to Day 1 (Screening/Baseline) Visit. Use of topical ocular steroids or non-steroidal anti-inflammatories (NSAIDs) within 1 week prior to Day 1 (Screening/Baseline) Visit. Use of these medications was not allowed during study participation. Use of nasal inhaled steroids was not allowed during the study. Bronchial steroids by inhaler were allowed; however, nebulized steroids were excluded. Topical dermal steroids were allowed except on the face.
16. Use of systemic non-steroidal anti-inflammatories (NSAIDs) within 24 hours prior to Day 1 (Screening/Baseline) Visit or any time during the study unless the patient had been on a steady (not as needed) treatment regimen for at least 2 months prior to entry and the therapy was continued throughout the study. Acetaminophen (e.g., Tylenol) PRN was allowed.
17. Any systemic or ocular disease or disorder, complicating factors or structural abnormality that would have negatively affected the conduct or outcome of the study (e.g., hepatitis, acute or chronic renal insufficiency or corneal anesthesia) or have represented in the opinion of the Investigator an undue risk to the patient.
18. Any immunosuppressive disorder (e.g., HIV-positive), or use of immunosuppressive therapy (including chemotherapy)
19. Known or suspected allergy or hypersensitivity to fluoroquinolones
20. Pregnant or lactating women, women who had a positive urine pregnancy test, or women of childbearing potential who were not using adequate birth control to prevent pregnancy
21. Participation in any other investigational clinical study within 30 days prior to study entry
22. Any patient who had a family member currently enrolled in this study
23. Any patient who was on staff at the investigational site or was a family member of staff personnel.

Additionally, the Medical Monitor could have declared any patient ineligible for a sound medical reason.

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Primary Efficacy Variable (s)

The primary efficacy variable was clinical cure at the Day 4 [EOT/Exit Visit (12-48 hours after the last dose)]. Clinical cure was attained if the sum of the 2 cardinal ocular signs of bacterial conjunctivitis (bulbar conjunctival injection and conjunctival discharge/exudate) was zero (i.e., normal or absent) at Day 4. The primary microbiological efficacy variable was the bacterial eradication rate at Day 4 [EOT/Exit Visit (12-48 hours after the last dose)].

Secondary Efficacy Variable (s)

The secondary efficacy variables were the eight individual signs and symptoms of bacterial conjunctivitis (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at Day 3 and Day 4 (EOT)/Exit Visits and sustained clinical cure at the Day 3 Visit. A cure for an individual ocular sign or symptom was attained if the score was zero (i.e., absent or normal) and remained zero (for Day 3 findings) throughout the rest of the study. Likewise, sustained clinical cure at the Day 3 Visit was attained if the score was zero (i.e., absent or normal) and remained zero throughout the rest of the study.

Primary Efficacy Analysis

The primary statistical objective of the study was to demonstrate that Moxifloxacin AF Ophthalmic Solution was superior to Moxifloxacin AF Vehicle in the treatment of bacterial conjunctivitis. Primary efficacy had two components, clinical and microbiological.

Investigators

Investigator	Investigator #	# of Patients Enrolled
Amin, Pranav, M.D. Yuba City, CA 95991	4155	0
Andrews, Wilson Jr., M.D. Woodstock, GA 30189	2355	6
Bacharach, Jason, M.D. Petaluma, CA 94954	2434	10
Bain, Russel, M.D. Spring Hill, FL 34609	5421	1
Baret, Eric, M.D. Carrollton, GA 30117	4640	0
Bean, James, M.D. Springboro, OH 45066	5483	15
Beck, William, M.D. Newton, KS 67114	5486	14
Berkowitz, Peter, M.D.	5473	3

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Pittsburgh, PA 15232		
Bernard, John V., M.D. Belvidere, NJ 07823	5422	6
Bibler, Mark, M.D. Vista, CA 92084	5432	9
Blahey, Maria, M.D. Beaumont, TX 77701	5787	3
Branch, James D., M.D. Winston Salem, NC 27101	3631	44
Calcagno, John, M.D. Gresham, OR 97030	5028	17
Cardona, David, M.D. Fresno, CA 93703	5487	0
Choi, Steve, M.D. Dayton, OH 45432	5396	33
Christie, William, M.D. Cranberry Township, PA 16066	3712	0
Chrostowski, Dariusz, M.D. Elmira, NY 14901	4912	0
Cibik, Lisa, M.D. West Mifflin, PA 15122	3900	0
Colquhoun, Jeffrey, M.D. Battle Creek, MI 49015	4529	0
Cottingham, Andrew, M.D. San Antonio, TX 78229	3349	15
Curry, Lawrence, D.O. Mishawaka, IN 46545	5409	12
Damian, David, M.D. Bryan, TX 77802	2734	3
Dao, Jung, M.D. Phoenix, AZ 85032	3920	49
Dawson, Peter, M.D. Houston, TX 77008	2678	9
Diaz, Carlos, M.D. Boerne, TX 78006	5219	0
Dorfman, Mark, M.D. Pembroke Pines, FL 33028	3440	1
El-Harazi, Sherif, M.D. Glendale, CA 91205	5213	30
Ericksen, Corey, D.O. Clinton, UT 84015	5423	49
Faulkner, William, M.D. Cincinnati, OH 45242	5214	0

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Feaver, Brian, M.D. Lake Jackson, TX 77566	4811	27
Firozvi, AsraShabana, M.D. Durham, NC 27704	5465	3
Flynn, William, M.D. San Antonio, TX 78229	5145	12
Garcia, Alberto, M.D.* Hahira, GA 31632	5488	4
George, Fred, M.D. Jonesboro, AR 72401	5410	7
Gira, Joseph, M.D. Des Peres, MO 63131	5459	0
Goldberg, Damien, M.D. Torrance, CA 90505	5489	17
Gonzales, Carlos, M.D. Houston, TX 77025	5460	32
Grossberg, Judith, M.D. Midlothian, VA 23113	5257	11
Gupta, Piyush, M.D. Colombus, OH 43214	5790	2
Hammond, Stephen Jr., M.D. Jackson, TN 38305	5403	0
Harris, Charles Lee, M.D. Savannah, GA 31405	5400	0
Harris-Ford, Laurie, M.D. Clarksville, TN 37043	5411	9
Hector, Richard, M.D. Bradenton, FL 34209	4779	1
Hillman, David, M.D. Chicago, IL 60634	4241	2
Hirschfield, Jeffrey, M.D. St. Petersburg, FL 33710	3568	42
Hitchcock, William, M.D. La Jolla, CA 92037	4663	26
Hoffman, Richard, M.D. Eugene, OR 97401	5490	0
Hudson, Claudia, M.D. Whitehouse Station, NJ 08889	5474	21
Huffman, D. Wade, M.D. Clarksville, TN 37043	5431	11
Hughes, Frank, M.D. Bossier City, LA 71111	5412	15
Jacobs, Michael, M.D.	5404	3

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Bogart, GA 30622		
Kang, Paul C., M.D. Chevy Chase, MD 20815	4822	0
Katzman, Barry, M.D. San Diego, CA 92115	2449	24
Kelly, Thomas F., M.D. Las Vegas, NV 89148	5167	7
Khamis, Sherif, M.D. Canoga Park, CA 91306	5495	49
Khurma, Sukhdev, M.D. Xenia, OH 45385	5491	5
Koch, Stanley, M.D. Morton, IL 61550	5092	14
Landis, Miles, M.D. Orange City, FL 32763	5526	19
Lane, Stephen, M.D. Stillwater , MN 55082	1201	1
Lin, Christopher, M.D. Redding, CA 96002	3975	21
Lothringer, Larry, M.D. San Antonio, TX 78215	5399	39
Luffey, Gary, M.D. Ruston, LA 71270	2123	22
Malhotra, Ranjan, M.D. St. Louis, MO 63131	4824	25
Marcadis, Isaac, M.D. West Palm Beach, FL 33409	5069	0
Mattas, Steven, M.D. Louisville, KY 40207	5793	0
Mazzone, Frank, M.D. San Luis Obispo, CA 93405	5495	18
McGuinn, Tracey, M.D. Chaska, MN 55318	5496	4
McLaurin, Eugene, M.D. Memphis, TN 38119	4011	2
Meier, Edward J., M.D. Mason, OH 45040	4755	2
Mijares-Zimmerman, Jennifer, M.D. Pace, FL 32571	5094	2
Montgomery, Jacob S., M.D. Walhalla, SC 29691	5301	0
Moyes, Andrew, M.D. Kansas City, MO 64154	4785	4

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Mullen, Julie, D.O. Erlander, KY 41018	5095	29
Nolen, Thomas, M.D. Columbiana, AL 35051	5066	0
Pendleton, Robert, M.D. Oceanside, CA 92056	4841	2
Perry, Patti, M.D. Yuma, AZ 85364	5512	1
Petermann, Scott, M.D.* Valdosta, GA 31602	5220	0
Pullman, John, M.D. Butte, MT 59701	5640	2
Qaqundah, Paul, M.D. Huntington Beach, CA 92647	5096	28
Raizman, Michael, M.D. Boston, MA 02114	1440	0
Rao, Sanjay, M.D. Chicago, IL 60601	5315	14
Rees, Peter, M.D. Haverhill, MA 01830	5523	1
Rubin, Jay, M.D. San Antonio, TX 78209	1725	0
Ruoff, Gary E., M.D. Kalamazoo, MI 49009	2332	0
Sanchez-Bal, Victoria, M.D. Bellflower, CA 90706	3495	17
Sawusch, Mark, M.D. Pacific Palisades, CA 90272	5398	9
Schenker, Howard, M.D. Rochester, NY 14618	1939	10
Scher, Colin, M.D. San Diego, CA 92123	5492	0
Senders, Shelly, M.D. Cleveland, OH 44121	5532	2
Shaw, Grady, M.D. Corsicana, TX 75110	5264	36
Shettle, Phillip Lee, D.O. Largo, FL 33770	3346	7
Silverstein, Steven M., M.D. Kansas City, MO 64133	3807	4
Smith, Christopher, M.D. Cortland, NY 13045	4888	0
Smith, Stephen E., M.D.	3988	6

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Fort Meyers, FL 33901		
Stanford, Richard, M.D. Oklahoma City, OK 73112	5785	4
Stein, Emil, M.D. Las Vegas, NV 89119	3851	15
Stewart, Jeffrey, M.D. Carrollton, TX 75010	5584	1
Sullivan, Timothy, M.D. Norwich, CT 06360	5265	10
Tachibana, Timothy, M.D. Fountain Valley, CA 92708	5493	29
Tauber, Joseph, M.D. Kansas City, MO 64111	1455	0
Tauber, Shachar, M.D. Springfield, MO 65804	4565	5
Torres, Nora, M.D. Houston, TX 77015	5511	0
Toyos, Rolando, M.D. Memphis, TN 38120	4753	3
Tsai, Clark, M.D. Concord, CA 94520	5418	32
Wallshein, Jay, M.D. Lake Worth, FL 33461	5397	15
Wapner, Francis J., M.D. Salt Lake City, UT 84124	1805	11
Wasserstrom, Jeffrey, M.D. La Mesa, CA 91942	1913	8
Wisman, Paul, M.D. Charlottesville, VA 22902	4131	24

*Dr. Scott Petermann replaced Dr. Alberto Garcia as the Principal Investigator.

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

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Treatment of bacterial conjunctivitis in patients ≥ 1 year of age.

6.1.1 Methods

Description of the clinical trial design is contained in Section 5.3.

6.1.2 Demographics

Patient Demographics

		Study	
		C-07-40	
Treatment Group		Moxi AF	Vehicle
Total enrollment in study		593	586
Race	White	463	488
	Black or African American	84	55
	Asian	18	8
	Native Hawaiian	3	1
	American Indian	6	6
	Other	14	21
	Multi-Racial	5	7
Age	28 days to 23 months	49	47
	2 to 11 years	174	184
	12 to 17 years	71	72
	18 to 64 years	257	230
	≥ 65 years	42	53
Sex	Male	240	248
	Female	353	338
Iris color	Brown	331	315
	Blue	147	150
	Hazel	74	75
	Green	38	44
	Grey	3	2
Culture positive	Yes	424	423
	No	169	163

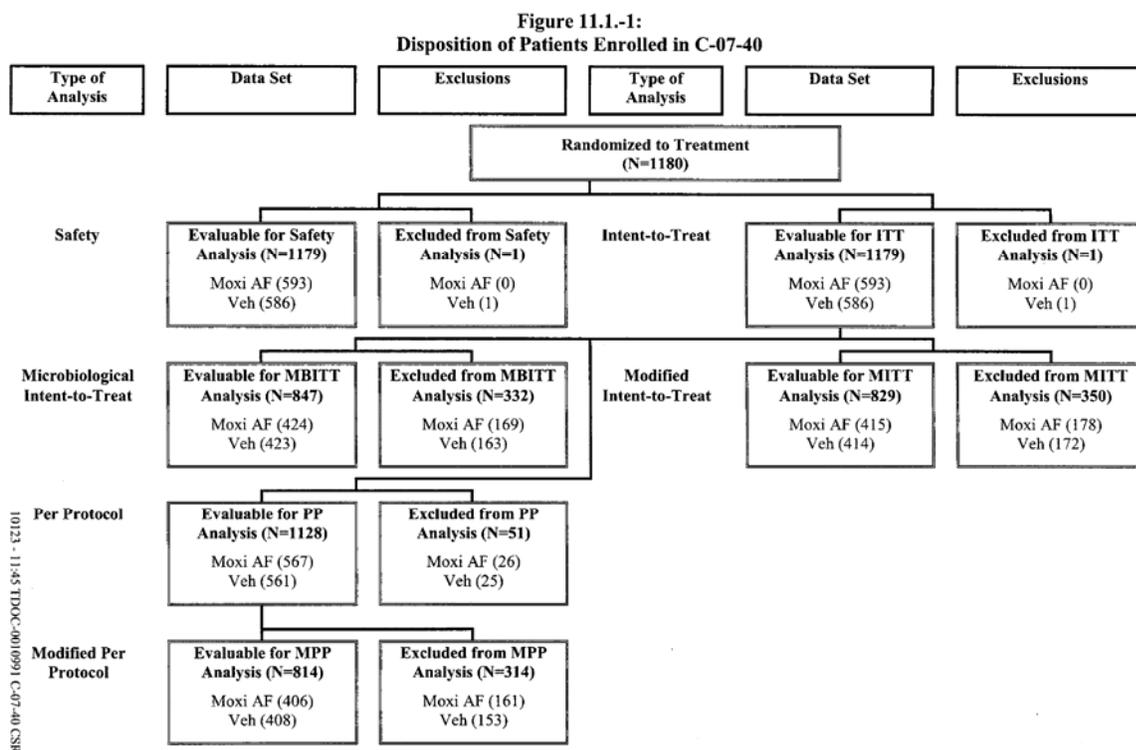
**Age Distribution by Treatment Group – All Clinical Studies
 (C-04-38, C-04-40, C-07-40)**

	Total N (%)	Moxi AF N (%)	Vigamox N (%)	Vehicle N (%)
Total	2535 (100.0)	1270 (100.0)	349 (100.0)	916 (100.0)
Age				
Infants (≥ 1 to < 2 months)*	8 (0.3)	1 (0.1)	2 (0.6)	5 (0.5)
Infants (≥ 2 to < 3 months)	4 (0.2)	3 (0.2)	0 (0.0)	1 (0.1)
Infants (≥ 3 to < 4 months)	7 (0.3)	3 (0.2)	0 (0.0)	4 (0.4)
Infants (≥ 4 to < 5 months)	11 (0.4)	10 (0.8)	0 (0.0)	1 (0.1)
Infants (≥ 5 to < 12 months)	77 (3.0)	41 (3.2)	3 (0.9)	33 (3.6)
Toddlers (12 to 23 months)	114 (4.5)	59 (4.6)	1 (0.3)	54 (5.9)
Children (2 to 11 years)	651 (25.7)	317 (25.0)	26(7.4)	308 (33.6)
Adolescents (12 to 17 years)	241 (9.5)	110 (8.7)	24 (6.9)	107 (11.7)
Adults (18 to 64 years)	1250 (49.3)	646 (50.9)	262 (75.1)	342 (37.3)
Elderly (65 years and older)	172 (6.8)	80 (6.3)	31 (8.9)	61 (6.7)

*Patients under 1 month of age were not enrolled in Studies C-04-38, C-04-40 and C-07-40.

6.1.3 Subject Disposition

Study C-07-40 Subject Disposition



10123 - 11-45 TDOCC-0010991 C-07-40 CSR

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for study C-07-40 was the clinical cure rate of the two ocular signs of bacterial conjunctival infection (bulbar conjunctival injection and conjunctival discharge/exudate) at the EOT/Exit Visit (Day 4). Clinical cure was attained when the sum of the two ocular signs was zero. The primary microbiological endpoint was the bacterial eradication rate at the EOT/Exit Visit (Day 4).

The primary statistical objective for study C-07-40 was to demonstrate that moxifloxacin AF was superior to vehicle in the treatment of bacterial conjunctivitis.

Analysis Populations:

Safety: All patients who received drug.

Intent-to-Treat (ITT): All patients who received drug and had at least one on-therapy visit.

Microbiological Intent-to-Treat (MBITT): All patients who received drug, had at least one on-therapy visit and were pathogen positive for bacteria on Day 1.

Modified Intent-to-Treat (MITT): All patients who received drug, had at least one on-therapy visit, met pre-randomization inclusion and exclusion criteria and were pathogen positive for bacteria on Day 1.

Per Protocol (PP): All patients who received drug, met pre-randomization inclusion and exclusion criteria and had baseline and test of cure (or exit if the patient exited from the study early) visits.

Modified Per Protocol (MPP): All patients who received drug, met pre-randomization inclusion and exclusion criteria, had baseline and test of cure (or exit if the patient exited from the study early) visits and were pathogen positive for bacteria on Day 1.

The planned primary efficacy endpoints for this study were clinical cure (bulbar conjunctival injection+0, normal and conjunctival discharge/exudate=0, absent) and microbiological success (bacterial eradication of pre-therapy pathogens) at the Day 4 [(EOT)/exit] Visit.

Study C-07-40

	Clinical Cure at Day 4				
	MBITT	ITT	MITT	PP	MPP
Moxifloxacin AF	265/424 (62.5%)	372/593 (62.7%)	261/415 (62.9%)	342/539 (63.5%)	243/383 (63.4%)
Vehicle	214/423 (50.6%)	310/586 (52.9%)	207/414 (50.0%)	285/529 (53.9%)	194/380 (51.1%)

p-value	0.0005	0.0006	0.0002	0.0015	0.0005
---------	--------	--------	--------	--------	--------

	Microbiological Success at Day 4		
	MBITT	MITT	MPP
Moxifloxacin AF	316/424 (74.5%)	308/415 (74.2%)	285/385 (74.0%)
Vehicle	237/423 (56.0%)	231/414 (55.8%)	220/384 (57.3%)
p-value	< 0.0001	< 0.0001	< 0.0001

Reviewer’s Comments:

The Agency informed the applicant during development that the MBITT population would be used for the efficacy evaluation. Moxifloxacin AF dosed two times a day demonstrates superiority to its vehicle in Study C-07-40 for clinical efficacy at Day 4 (p= 0.0005). The clinical cure rate for Moxifloxacin AF was 62.5%. The ITT, MITT, PP and MPP population results are consistent with the MBITT population.

Microbiological efficacy was demonstrated at Day 4 in the MBITT, MITT, and MPP populations (< 0.0001). The microbiological eradication rate for moxifloxacin AF was 74.5%.

6.1.5 Analysis of Secondary Endpoints(s)

The planned secondary endpoints for this study included the eight individual sign and symptom cure rates (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at Day 3 and Day 4 (EOT)/Exit Visits and sustained clinical cure at the Day 3 Visit. A cure for an individual ocular sign or symptom was attained if the score was zero (i.e., absent or normal) and remained zero (for Day 3 findings) throughout the rest of the study. Likewise, sustained clinical cure at the Day 3 Visit was attained if the score was zero (i.e., absent or normal) and remained zero throughout the rest of the study.

After adjusting for multiplicity, bulbar conjunctival injection in the MBITT and MITT populations and conjunctival discharge/exudate in the ITT population demonstrated statistical significance. No other secondary endpoints achieved statistical significance.

Reviewer’s Comments:

Significance of these two secondary endpoints is expected since bulbar conjunctival injection and conjunctival discharge/exudate are the 2 cardinal signs of bacterial conjunctivitis.

6.1.6 Other Endpoints

Exploratory Analyses included and evaluation of an earlier clinical cure at Day 3. Clinical cure was attained if the sum of the 2 cardinal ocular signs of bacterial conjunctivitis was zero (i.e., normal or absent) and remained zero throughout the course of the study.

Study C-07-40

	Clinical Cure at Day 3				
	MBITT	ITT	MITT	PP	MPP
Moxifloxacin AF	71/424 (16.7%)	101/593 (17.0%)	71/415 (17.1%)	99/561 (17.6%)	72/401 (18.0%)
Vehicle	56/423 (13.2%)	88/586 (15.0%)	53/414 (12.8%)	84/551 (15.2%)	53/398 (13.3%)
p-value	0.1529	0.3457	0.0822	0.2801	0.0711

Reviewer's Comments:

Moxifloxacin AF failed to demonstrate clinical efficacy versus its vehicle at Day 3 in all study populations.

6.1.7 Subpopulations

The primary efficacy endpoint (clinical cure and microbiological success at Day 4 (EOT)/Exit Visit) were analyzed separately by investigator and for each of the following demographic subgroups in study C-07-40: age (28 days to 23 months, 2-11 years, 12-17 years, 18-64 years and age ≥ 65), sex, race, ethnicity, iris color, affected eye(s) and study eye. These analyses were performed in the ITT, MBITT, MITT, PP, and MPP data sets.

MBITT – Clinical Cure at Day 4 (EOT) - Study C-07-40

<i>Age</i>	<i>Treatment</i>	<i>Total</i>	<i>Clinical Cure</i>		<i>p-value</i>
		<i>N</i>	<i>N</i>	<i>%</i>	
<i>28 days – 23 months</i>	<i>Moxifloxacin AF</i>	<i>44</i>	<i>33</i>	<i>75.0</i>	<i>0.0598</i>
	<i>Vehicle</i>	<i>43</i>	<i>24</i>	<i>55.8</i>	
<i>2-11 years</i>	<i>Moxifloxacin AF</i>	<i>129</i>	<i>96</i>	<i>56.0</i>	<i>0.0017</i>
	<i>Vehicle</i>	<i>134</i>	<i>75</i>	<i>51.4</i>	
<i>12-17 years</i>	<i>Moxifloxacin AF</i>	<i>43</i>	<i>24</i>	<i>55.8</i>	<i>0.8153</i>
	<i>Vehicle</i>	<i>45</i>	<i>24</i>	<i>53.3</i>	
<i>18-64 years</i>	<i>Moxifloxacin AF</i>	<i>175</i>	<i>95</i>	<i>54.3</i>	<i>0.2847</i>
	<i>Vehicle</i>	<i>159</i>	<i>77</i>	<i>48.4</i>	
<i>≥ 65 years</i>	<i>Moxifloxacin AF</i>	<i>33</i>	<i>17</i>	<i>51.5</i>	<i>0.1125</i>
	<i>Vehicle</i>	<i>42</i>	<i>14</i>	<i>33.3</i>	

MBITT – Microbiological Success at Day 4 (EOT) - Study C-07-40

<i>Age</i>	<i>Treatment</i>	<i>Total</i>		<i>Success</i>		<i>p-value</i>
		<i>N</i>	<i>N</i>	<i>%</i>		
<i>28 days – 23 months</i>	<i>Moxifloxacin AF</i>	<i>44</i>	<i>34</i>	<i>77.3</i>		<i>0.0016</i>
	<i>Vehicle</i>	<i>43</i>	<i>19</i>	<i>44.2</i>		
<i>2-11 years</i>	<i>Moxifloxacin AF</i>	<i>129</i>	<i>107</i>	<i>82.9</i>		<i><0.0001</i>
	<i>Vehicle</i>	<i>134</i>	<i>78</i>	<i>58.2</i>		
<i>12-17 years</i>	<i>Moxifloxacin AF</i>	<i>43</i>	<i>30</i>	<i>69.8</i>		<i>0.5422</i>
	<i>Vehicle</i>	<i>45</i>	<i>34</i>	<i>75.6</i>		
<i>18-64 years</i>	<i>Moxifloxacin AF</i>	<i>175</i>	<i>122</i>	<i>69.7</i>		<i>0.0324</i>
	<i>Vehicle</i>	<i>159</i>	<i>93</i>	<i>58.5</i>		
<i>≥ 65 years</i>	<i>Moxifloxacin Af</i>	<i>33</i>	<i>23</i>	<i>69.7</i>		<i>0.0009</i>
	<i>Vehicle</i>	<i>42</i>	<i>13</i>	<i>31.0</i>		

Reviewer’s Comments:

In general, the results of the subgroup analysis for Study C-07-40 follow the same trend as the overall efficacy analysis. The primary endpoint of clinical cure and microbiological success at Day 4 appears to be driven by the 2-11 age group subset.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The concentration of 0.5% moxifloxacin was chosen for Moxifloxacin AF based on the efficacy and safety of Vigamox. The modified formulation contains a xanthan gum (b) (4) of the product on the ocular surface with the objective of maintaining similar efficacy to Vigamox with reduced dosing (i.e. two times a day versus three times a day).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study C-07-40, patients were evaluated at the End-of-Therapy Visit approximately 12- 48 hours following the last dose and in Studies C-04-38 and C-04-40, patients were evaluated at a Test-of-Cure Visit approximately 60-90 hours following the last dose. No evidence of tolerance or withdrawal effects was detected.

6.1.10 Additional Efficacy Issues/Analyses

Clinical Cure by Organism for patients Treated with Moxifloxacin AF
 Studies C-04-38, C-04-40, and C-07-40 Combined (MBITT Population)

Organism	Total (N)	Clinical Cure (n)	Clinical Failure (n)	Eradication Rate (%)
Gram - positive				
<i>Aerococcus viridans</i> *	6	6	0	100
<i>Corynebacterium macginleyi</i> *	7	7	0	100
<i>Enterococcus faecalis</i> *	6	6	0	100
<i>Micrococcus luteus</i> *	6	6	0	100
<i>Staphylococcus arlettae</i> *	8	8	0	100
<i>Staphylococcus aureus</i>	38	36	2	95
<i>Staphylococcus capitis</i> ¹	25	24	1	96
<i>Staphylococcus epidermidis</i>	156	145	11	93
<i>Staphylococcus haemolyticus</i>	13	10	3	77
<i>Staphylococcus hominis</i> ²	10	10	0	100
<i>Staphylococcus saprophyticus</i> *	6	6	0	100
<i>Staphylococcus warneri</i> *	10	8	2	80
<i>Streptococcus mitis</i> *	11	9	2	82
<i>Streptococcus pneumoniae</i>	43	39	4	91
<i>Streptococcus parasanguinis</i> *	5	5	0	100
Gram - negative				
<i>Escherichia coli</i> *	6	5	1	83
<i>Haemophilus influenzae</i>	109	100	9	92
<i>Klebsiella pneumoniae</i> *	8	8	0	100
Anaerobe				
<i>Propionibacterium acnes</i>	152	139	13	91
Other bacteria				
<i>Chlamydia trachomatis</i> *	5	5	0	100

* Efficacy for this organism was found in fewer than 10 infections.

¹ Includes *Staphylococcus capitis subspecies capitis* (3), *S. capitis* (22); eradication rate 100% and 96 % respectively.

² Includes *Staphylococcus hominis ss. novobiosepticus* (4), *S. hominis* (6); eradication rate 100%.

7 Review of Safety

Safety Summary

7.1 Methods

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
C-07-12 Single topical ocular dose conjunctiva /aqueous humor PK study	Single-dose, double-masked, randomized, parallel group	Cataract surgery patients	Moxifloxacin AF ophthalmic solution Vigamox	1 drop 1 drop	Single dose	130
C-05-15 Multiple topical ocular dosing systemic PK/safety study	Multiple-dose, double-masked, randomized, vehicle – controlled, parallel-group	Healthy adult male and female volunteers	Moxifloxacin AF ophthalmic solution Vehicle	1 drop BID OU 1 drop BID OU	4 days with final dose on morning of Day 5	30
C-04-38 Safety/efficacy study	Prospective, randomized, vehicle-controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution Vehicle	1 drop BID OU 1 drop BID OU	3 days	661 (345 culture positive diagnosed eye)
C-04-40 Safety/efficacy study	Prospective, randomized, active-controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution <u>and</u> Vehicle Vigamox	1 drop BID OU <u>and</u> 1 drop BID OU 1 drop TID OU	3 days	695 (382 culture positive diagnosed eye)
C-07-40 Safety/efficacy study	Prospective, randomized, vehicle-controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution Vehicle	1 drop BID OU	3 days	1179 (847 culture positive diagnosed eye)

7.1.2 Categorization of Adverse Events

Routine clinical testing was required to establish the safety of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.). This was adequately addressed in the design and conduct of the clinical trials. All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

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

Due to the size of the data base, the pooled data was used in the analysis of common adverse events. Adverse events for each study were also evaluated individually.

7.2 Adequacy of Safety Assessments

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

A total of 1355 patients were exposed to moxifloxacin AF during development.

Overview of Exposure to Study Drug by Protocol

Protocol Number	Safety N	Moxi AF	Vigamox	Vehicle
C-07-40	1177	593		586
C-04-38	661	331		330
C-04-40	695	346	349	
C-05-15	30	20		10
C-07-12	130	65	65	

The age distribution of the patients exposed to moxifloxacin during development is as follows:

Age group	Number exposed
28 days to 23 months	117
2 to 11 years	317
12 to 17 years	109
18 to 64 years	675
65 years or older	127

Reviewer's Comments:

The majority (58-95.7%) of patients in each age group were exposed to moxifloxacin AF for 3 days with another 2-5% exposed to a total of 4 days of drug.

7.2.2 Explorations for Dose Response

Moxifloxacin AF was administered in one dose level (1 drop twice a day for three days) for each of the phase 3 studies. No dose response information was obtained.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with Moxifloxacin AF.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

Based on in vitro studies conducted on moxifloxacin and contained in the original NDA, moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 and therefore is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

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

The adverse events reported during the development of moxifloxacin AF are consistent with other topical quinolones. The assessment of these adverse events in the clinical trials were adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the clinical development of moxifloxacin AF.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported during the clinical development of moxifloxacin AF.

7.3.3 Dropouts and/or Discontinuations

Reason for Discontinuation	C-07-40		C-04-38		C-04-40	
	Moxi AF	Vehicle	Moxi AF	Vehicle	Moxi AF	Vigamox
Adverse event	1	6	5	5	3	1
Lost to follow-up	3	9	3	6	24	25
Patient's decision unrelated to an adverse event	3	7	5	5	2	2
Noncompliance	0	0	1	8	0	1
Treatment Failure	6	10	7	32	7	13
Other	1	1	1	4	0	0

Moxi AF = Moxifloxacin AF

A Table of the adverse events associated with the discontinuations from each of the clinical study is presented below.

Adverse Events Associated with Discontinuation – Study C-07-40

Patient	Age	Sex	Treatment	Onset day	Adverse event
9507	76	F	Moxifloxacin AF	2	Eye irritation

Adverse Events Associated with Discontinuation – Study C-04-38

Patient	Age	Sex	Treatment	Onset day	Adverse event
1720	48	F	Moxifloxacin AF	1	Foreign body sensation, increased lacrimation, conjunctival disorder
2005	32	M	Moxifloxacin AF	2	gonorrhea
1314	19	F	Moxifloxacin AF	2	Streptococcal pharyngitis
2218	1	M	Moxifloxacin AF	5	Sinusitis
102	15	M	Moxifloxacin AF	3	Conjunctivitis
405	1	M	Vehicle	2	Otitis Media
1312	3	M	Vehicle	4	Otitis media
2126	2	M	Vehicle	1	Periorbital cellulitis
926	42	F	Vehicle	5	conjunctivitis
104	41	M	Vehicle	4	Uveitis

Adverse Events Associated with Discontinuation – Study C-04-40

Patient	Age	Sex	Treatment	Onset day	Adverse event
3413	21	M	Moxifloxacin AF	2	Conjunctival edema, eyelid edema, ocular hyperemia
2422	41	M	Moxifloxacin AF	6	Conjunctival ulcer
4007	9	M	Moxifloxacin AF	1	Rhinitis, corneal opacity, punctate keratitis, nasal congestion, pyrexia
3408	24	M	Vigamox	3	Conjunctival edema, eye pruritus, eyelid edema

7.3.4 Significant Adverse Events

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

7.3.5 Submission Specific Primary Safety Concerns

N/A – No specific safety issues identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

**Common Adverse Events (rate ≥ 1%) – Safety Population
 (Studies C-04-38, C-04-408, C-05-15, C-07-12, C-07-40 Pooled)**

Adverse Event	Moxifloxacin AF N=1355		Vigamox N=414		Vehicle N=926	
	N	%	N	%	N	%
<i>Eye disorder</i>						
Eye irritation	16	1.2	5	1.2	6	0.6
Conjunctivitis	14	1.0	2	0.5	13	1.4
Eye Pain	14	1.0	7	1.7	5	0.5
Eye pruritis	5	0.4	5	1.2	2	0.2
Punctate keratitis	5	0.4	5	1.2	2	0.2
<i>General disorders and administration</i>						

Clinical Review
 Lucious Lim, M.D., M.P.H.
 NDA 22-428
 Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

<u>site conditions</u>						
Pyrexia	16	1.2	7	1.7	6	0.6
<u>Infections and infestations</u>						
Conjunctivitis bacterial	8	0.6			22	2.4
Otitis media	4	0.3			10	1.1
<u>Nervous system disorders</u>						
Headache	8	0.6	2	0.5	10	1.1

Common Adverse Events (rate ≥ 1%) – Safety Population – study C-07-40

Adverse Event	Moxifloxacin AF N=331		Vehicle N=330	
	N	%	N	%
<u>Eye disorders</u>				
Conjunctivitis	4	0.7	8	1.4
<u>General disorders and administration site conditions</u>				
Pyrexia	7	1.2	2	0.3
<u>Infections and infestations</u>				
Conjunctivitis bacterial	8	1.3	22	3.8

Common Adverse Events (rate ≥ 1%) – Safety Population – study C-04-38

Adverse Event	Moxifloxacin AF N=331		Vehicle N=330	
	N	%	N	%
<u>Eye disorders</u>				
Conjunctivitis	5	1.5	5	1.5
<u>Infections and infestations</u>				
Upper respiratory tract infection	6	1.8	5	1.5
Otitis media	2	0.6	6	1.8
<u>Nervous system disorders</u>				

Clinical Review
 Lucious Lim, M.D., M.P.H.
 NDA 22-428
 Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Headache	0	0	6	1.8
<i>General disorders and administration site conditions</i>				
Pyrexia	2	0.6	4	1.2

Common Adverse Events (rate ≥ 1%) – Safety Population – study C-04-40

Adverse Event	Moxifloxacin AF N=346		Vigamox N=349	
	N	%	N	%
<i>Eye disorders</i>				
Eye irritation	8	2.3	5	1.4
Eye pain	8	2.3	7	2.0
Conjunctivitis	5	1.4	2	0.6
Punctuate keratitis	5	1.4	5	1.4
Eye pruritus	1	0.3	5	1.4
<i>General disorders and administration site conditions</i>				
Pyrexia	7	2.0	7	2.0

7.4.2 Laboratory Findings

Clinical laboratory evaluations were analyzed in one pharmacokinetic study (C-05-15) which involved 30 healthy male and female patients (19 to 73 years of age). Laboratory test including hematology, blood chemistry and urinalysis results were evaluated in all patients at baseline and exit.

There were statistically significant changes from baseline for both moxifloxacin AF and the vehicle in several hematology and blood chemistry parameters. However, these changes were not clinically relevant and each remained within the normal range.

There were no statistically significant changes in urinalysis measurements for either moxifloxacin AF or the vehicle.

7.4.3 Vital Signs

Cardiovascular parameters (pulse and blood pressure) were measured at screening, day 1 and the exit visit. Any clinically relevant changes from baseline were reported as an adverse event. No adverse events were reported for the cardiovascular parameters during the study. No clinically relevant changes in cardiovascular parameters were observed. No clinically relevant differences between the treatment groups were identified.

7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECGs were obtained at baseline and the exit visit. There were no clinically relevant changes reported within groups or between groups for moxifloxacin and the vehicle group.

7.4.5 Special Safety Studies/Clinical Trials

N/A – There were no special safety studies conducted for this product.

7.4.6 Immunogenicity

N/A – Immunogenicity testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Moxifloxacin AF was administered in one dose level (1 drop twice a day for three days) for each of the phase 3 studies. No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

N/A – Moxifloxacin does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

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

7.5.4 Drug-Disease Interactions

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

7.5.5 Drug-Drug Interactions

No drug interactions were reported in any clinical study involving Moxifloxacin AF.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted. In addition, long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. An accelerated study with initiators and promoters was conducted in rats and moxifloxacin was not found to be carcinogenic. (See original review/label for Vigamox).

7.6.2 Human Reproduction and Pregnancy Data

The clinical study protocols involving moxifloxacin AF excluded the participation of pregnant or breast-feeding females. No information was obtained on its use in these populations.

7.6.3 Pediatrics and Assessment of Effects on Growth

Based on the review of the original NDA for Vigamox, there is no evidence that the ophthalmic administration of moxifloxacin has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No information is available on overdosage in humans. No reports of overdose were received during the clinical studies of moxifloxacin AF. In an oral (gavage) monkey study of moxifloxacin, doses up to 15mg/kg/day did not produce any toxicity. This dose is at least ten times higher than the accidental dose of one bottle of moxifloxacin AF, 5 mg/mL for a 10 kg child.

There was no evidence of drug abuse reported in the clinical trials. And there were no reports of withdrawal or rebound phenomena.

7.7 Additional Submissions / Safety Issues

The four-month safety update was received on September 28, 2010. There was no new information to report.

8 Postmarket Experience

Moxifloxacin AF is not marketed in any country. Moxifloxacin hydrochloride ophthalmic solution, 0.5% base is approved in more than 50 countries. It was approved in the U.S. in 2003.

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 22-428

Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

The sponsor has received 471 spontaneous adverse event reports worldwide associated with moxifloxacin. Thirty-five (35) were considered serious. The spontaneous postmarketing reports for moxifloxacin are consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with moxifloxacin.

9 Appendices

9.1 Literature Review/References

N/A – An independent literature review was not conducted for this application.

9.2 Labeling Recommendations

See labeling recommendations which follow in the attached label.

9.3 Advisory Committee Meeting

N/A – An advisory committee meeting is not required for this application.

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

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

/s/

LUCIOUS LIM
11/19/2010

WILLIAM M BOYD
11/19/2010

Comparison of Compositions of Moxifloxacin AF and Vigamox

Component	% Composition	
	Moxifloxacin AF	Vigamox
Moxifloxacin hydrochloride	0.545	Same
Xanthan gum	(b) (4)	(b) (4)
Sodium chloride		
Boric acid		
Sorbitol		
Tyloxapol		
Hydrochloric acid and/or sodium hydroxide	Adjust pH to 7.4	Adjust to pH 6.8
Purified water	(b) (4)	(b) (4)

The formulation of moxifloxacin used in the clinical studies is the same as the one intended for marketing.

2. Background

Alcon's proposed Phase 3 development program for moxifloxacin AF ophthalmic solution was discussed with the Agency in a Pre-IND/End of Phase 2 meeting on March 3, 2005. Alcon subsequently submitted Special Protocol Assessment requests for study C-04-38 and C-04-40, to which the Agency responded with comments on June 22, 2005. Comments on both studies were provided to Alcon. A Pre-NDA meeting package containing a summary of efficacy results from these studies was submitted to the Agency and comments were discussed at the Pre-NDA meeting on April 8, 2008. The new formulation of moxifloxacin is not marketed in any other country.

3. CMC

DRUG SUBSTANCE:

The applicant holds an approved NDA 21-598 on Vigamox, an ophthalmic solution containing the same drug substance. The drug substance information provided in NDA 21-598 is acceptable for the current application.

DRUG PRODUCT:

Moxifloxacin alternative formulation ophthalmic solution, 0.5% (Moxifloxacin AF) is a sterile, ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride, equivalent to 0.5% moxifloxacin. The proposed formulation has been modified (b) (4) with similar efficacy to Vigamox but with a less frequent dosing regimen from TID to BID. The product will be packaged in a natural, low density polyethylene (LDPE) bottle with a polyethylene (LDPE) natural dispensing plug and a tan polypropylene (PP) closure.

Division Director Review
Wiley A. Chambers M.D.
NDA 22-428
moxifloxacin hydrochloride ophthalmic solution, 0.5% as base

No (b) (4) is used in the proposed formulation. As with the marketed Vigamox product, the applicant has stated that the new formulation of moxifloxacin ophthalmic solution maintains adequate (b) (4) to meet USP (b) (4) effectiveness requirements in the absence of a (b) (4) agent.



All facilities were found acceptable for NDA 22-428 by Compliance as attached in EER at the end of the second CMC review.

4. Nonclinical Pharmacology/Toxicology

Daily topical application of the drug product to rabbits for up to one month was not associated with ocular inflammation, irritation, or toxicity. Higher concentrations of moxifloxacin (1%, 1.5%) in the same AF vehicle did not cause inflammation, but microscopic evaluation indicated signs of minor irritation in the lower conjunctiva and third eyelid. Ophthalmic examination (biomicroscopy/slit lamp, indirect ophthalmoscopy) did not reveal any changes associated with Moxifloxacin AF treatment at concentrations up to 1.5%. Moxifloxacin AF, 0.5%, did not impede wound healing in rabbits when applied following a keratectomy.

Systemic availability of moxifloxacin was very low in human subjects when the drug product was applied to both eyes twice daily for 4 days, then once on Day 5 (C_{max} 0.977 ± 0.673 ng/mL; AUC 8.17 ± 5.31 ng·hr/mL).

The genotoxic profile of moxifloxacin is comparable to other fluoroquinolones. It was mutagenic in one of 5 bacterial strains used for the Ames test (TA 102) and clastogenic in a chromosome aberration assay using cultured cells. It did not induce unscheduled DNA synthesis *in vitro* and was negative in a mouse micronucleus test *in vivo*. Moxifloxacin had no effect on fertility in rats at systemic doses far above those that can be achieved using a topical ophthalmic route. It was not teratogenic in rats and monkeys given oral doses far above the highest recommended total daily human ophthalmic dose.

5. Clinical Pharmacology/Biopharmaceutics

The extent of systemic exposure to moxifloxacin following topical ophthalmic administration of the new formulation of moxifloxacin was evaluated in a double-masked, vehicle-controlled, parallel-group, multiple-dose pharmacokinetic (PK) study in healthy adults (Study C-05-15). The clinical pharmacology findings from this study are summarized as follows:

- Following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days, a mean peak plasma concentration of 0.977 ± 0.673 ng/mL (range: 0.267 to 3.19 ng/mL) was observed within approximately one hour.
- Moxifloxacin concentrations declined in a monophasic manner with terminal half-lives ranging from 7.6 to 27.3 hours (mean half life: 16.6 ± 5.5 hours) in healthy subjects.
- Steady-state following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% was achieved between 3 to 4 days. The estimated accumulation ratio was 2.5.
- C_{max} and AUC_{0-8} for moxifloxacin following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days were approximately 36% and 45%, respectively, of the C_{max} and AUC_{0-8} observed following TID dosing for 5 days with the previously approved moxifloxacin ophthalmic formulation VIGAMOX.
- Moxifloxacin C_{max} following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days is approximately 0.02% of that achieved with the oral formulation of moxifloxacin hydrochloride (C_{max} values: Moxifloxacin AF, $0.977 \pm$

Division Director Review
Wiley A. Chambers M.D.
NDA 22-428
moxifloxacin hydrochloride ophthalmic solution, 0.5% as base

0.88 ng/mL versus AVELOX, 4.5 ± 0.5 µg/mL). These findings suggest a wide margin of safety for Moxifloxacin AF ophthalmic solution.

Based on the assessment of systemic exposure information for the drug product from a multiple-dose PK study in healthy adult male and female volunteers, the regulatory requirement for submission of in vivo bioavailability data has been adequately addressed.

6. Sterility Assurance

The integrity of the container/closure system for stability samples was demonstrated by successful sterility testing of each of the three primary stability lots of each of the (b) (4) and 3ml fill sizes (lot numbers SLN-0363, SLN-0365, SLN-0366, SLN-0368, SLN-0369, SLN-0371).

In addition, microbial ingress tests were conducted. For each of three validation runs, the challenged units were negative for growth. Positive controls were confirmed for E. coli growth, and negative controls showed no growth. Acceptable TSB growth promotion testing (< 100 CFU/ml E. coli) was performed. Plate counts were used to confirm the pre- and post-exposure microbial challenge (pre = 8.5 to 9.7×10^7 CFU/ml; post = 7.5 to 9.2×10^7 CFU/ml).

The drug product does not contain any traditional (b) (4) and the Applicant describes it as (b) (4) effectiveness testing was conducted on the six stability batches (3 lots of each fill size - lot numbers SLN-0363, SLN-0365, SLN-0366, SLN-0368, SLN-0369, SLN-0371).

Test data indicated that the drug product met or exceeded the USP <51> acceptance criteria for antimicrobial effectiveness. For the six lots tested at the three time periods, the drug product exhibited the following ranges for the reduction of organism counts:

Organism	Log10 unit reduction of microorganisms after		
	7 days	14 days	28 days
S. aureus (ATCC 65338)	4.8-5.4	4.8-5.4	4.8-5.4
P. aeruginosa (ATCC 9027)	4.6-5.4	4.6-5.4	4.6-5.4
E. coli (ATCC 8739)	4.9-5.4	4.9-5.4	4.9-5.4
C. albicans (ATCC 10231)	1.3-2.8	2.3-4.2	4.1-5.5
A. niger (ATCC 16404)	0.8-1.7	2.1-4.4	3.9-4.4

These results indicate the (b) (4) nature of the drug product formulation. Such product development study results mitigate the lack of a routine release assay for (b) (4) effectiveness.

7. Clinical/Statistical - Efficacy

This application contained two safety and efficacy trials. Study C-04-38 was a two-arm superiority trial comparing moxifloxacin to vehicle; C-04-40 was a non-inferiority trial which compared the new formulation to the currently marketed Vigamox. Study C-04-38 was

considered to be the most crucial for determining the efficacy of this product since the non-inferiority margin for study C-04-40 essentially requires the new formulation to be superior to Vigamox.

The primary clinical efficacy variable in Study C-04-38 was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection (bulbar conjunctival injection and conjunctival discharge/exudate). Clinical cure was attained when the sum of the two cardinal ocular signs was zero (i.e., normal or absent) at Day 7. The primary microbiological efficacy variable was the bacterial eradication rate at the Exit visit.

The primary clinical efficacy variable in Study C-04-40 was clinical cure. Clinical cure was achieved when the sum of the ratings for the cardinal ocular signs (bulbar conjunctival injection and conjunctival discharge/exudate) was zero (i.e. normal or absent) at the TOC (test of cure) visit (Day 7). The primary microbiological efficacy variable was microbiological success. Microbiological success was achieved when the pre-therapy pathogens were eradicated at TOC.

Analyses of Endpoints

Study C-04-38

	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	129 (72.5%)	128 (72.3%)	105 (75%)
Vehicle	113 (67.7%)	111 (67.3%)	88 (66.2%)
p-value	0.3295	0.3097	0.1089

	Microbiological Success at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	150 (84.3%)	149 (84.2%)	115 (82.7%)
Vehicle	110 (65.9%)	109 (66.1%)	90 (67.7%)
p-value	< 0.0001	0.0001	0.0039

The Agency informed Alcon during development that the Microbiological Intent-to-Treat¹ (MBITT) population would be used for the efficacy evaluation. Study C-04-38 failed to demonstrate efficacy for clinical cure at day 7. The Modified Intent-to-Treat² (MITT) and Modified Per Protocol³ (MPP) population results are consistent with the MBITT population.

¹ Microbiological Intent-to-Treat (MBITT): All patients who received drug, had at least one on-therapy visit and were pathogen positive for bacteria on Day 1.

² Modified Intent-to-Treat (MITT): All patients who received drug, had at least one on therapy visit, met pre-randomization inclusion and exclusion criteria and were pathogen positive for bacteria on Day 1.

³ Modified Per Protocol (MPP): All patients who received drug, met pre-randomization inclusion and exclusion criteria, had baseline and test of cure (or exit if the patient exited from the study early) visits and were pathogen positive for bacteria on Day 1.

Study C-04-40

	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	152 (80.4%)	150 (80.2%)	103 (84.4%)
Vigamox	163 (84.5%)	161 (84.3%)	108 (85.7%)
p-value	0.30	0.3	0.78
Delta	-4.1	-4.1	-1.3
LCL	-11.65	-11.78	-10.16
UCL	3.62	3.62	7.59

	Microbiological Success at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	165 (87.3%)	163 (87.2%)	112 (92.6%)
Vigamox	173 (89.6%)	171 (89.5%)	115 (92%)
p-value	0.48	0.47	0.87
Delta	-2.3	-2.3	0.6
LCL	-8.74	-8.8	-6.11
UCL	4.07	4.1	7.23

Alcon evaluated the data based on a non-inferiority margin of 15%. The Division does not agree that this is a justifiable margin based on available clinical trial data. Initial review of the available efficacy data suggests that an acceptable non-inferiority margin for topical anti-infectives may be in the range of 2%-6%. The results of this trial suggest that the new formulation of moxifloxacin is inferior to Vigamox for both clinical cure and microbiological success.

Additionally, the dosing regimen used in this trial for Vigamox is inconsistent with the regimen use in the approval for this product. The clinical trials conducted to establish the efficacy of Vigamox were conducted with the drug dosed for 4 days. Clinical cure rates at the end-of-therapy visit (day5) ranged from 66-69% and 83-87% at test of cure (day 7). In the current study (C-04-40) Vigamox is dosed for only 3 days in the comparator arm. This is not the optimum dosing frequency and is not the regimen used in the clinical trials to establish efficacy. The clinical cure rate is 58% at the end-of-therapy (day 4) and approximately 84-85% at the test-of-cure visit (day 7).

Clinical Microbiology Review

Data from the two Phase 3 clinical trials submitted in support of the Application suggest that the new formulation of moxifloxacin ophthalmic solution, 0.5% is effective in eradicating the principle pathogens associated with bacterial conjunctivitis. With the exception of *Haemophilus influenzae* (eradication 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

Division Director Review
 Wiley A. Chambers M.D.
 NDA 22-428
 moxifloxacin hydrochloride ophthalmic solution, 0.5% as base

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. 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).

8. Safety

Both Study C-04-38 and Study C-04-40 were used in the safety analysis. Study C-05-15, a multiple-dose, double-masked, randomized, vehicle -controlled, parallel-group pharmacokinetic study in 30 subjects was also used in the safety analysis. A total of 697 patients were exposed to moxifloxacin AF during development.

Exposure to Study Drug by Protocol

Protocol Number	Safety N	Moxifloxacin AF	Vigamox	Vehicle
C-04-38	661	331		330
C-04-40	695	346	349	
C-05-15	30	20		10

Exposure to Study Drug by Age Group

Age group	Number exposed
28 days to 23 months	68
2 to 11 years	143
12 to 17 years	38
18 to 64 years	399
65 years or older	39

Common Adverse Events (rate $\geq 1\%$) – Safety Population – Study C-04-38

Adverse Event	Moxifloxacin AF N=331		Vehicle N=330	
	N	%	N	%
<i>Eye disorders</i>				
Conjunctivitis	5	1.5	5	1.5
<i>Infections and infestations</i>				
Upper respiratory tract infection	6	1.8	5	1.5

Division Director Review
 Wiley A. Chambers M.D.
 NDA 22-428
 moxifloxacin hydrochloride ophthalmic solution, 0.5% as base

Otitis media	2	0.6	6	1.8
<i>Nervous system disorders</i>				
Headache	0	0	6	1.8
<i>General disorders and administration site conditions</i>				
Pyrexia	2	0.6	4	1.2

Common Adverse Events (rate ≥ 1%) – Safety Population – Study C-04-40

Adverse Event	Moxifloxacin AF N=346		Vigamox N=349	
	N	%	N	%
<i>Eye disorders</i>				
Eye irritation	8	2.3	5	1.4
Eye pain	8	2.3	7	2.0
Conjunctivitis	5	1.4	2	0.6
Punctuate keratitis	5	1.4	5	1.4
Eye pruritus	1	0.3	5	1.4
<i>General disorders and administration site conditions</i>				
Pyrexia	7	2.0	7	2.0

POSTMARKETING EXPERIENCE

This drug product is not marketed in any country. Other formulations of moxifloxacin hydrochloride ophthalmic solution, 0.5% base are approved in more than 50 countries including the US (approved in 2003). Alcon has received 471 spontaneous adverse event reports worldwide associated with moxifloxacin. Thirty-five (35) were considered serious. The spontaneous postmarketing reports for moxifloxacin are consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with moxifloxacin.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for moxifloxacin hydrochloride ophthalmic solution 0.5%.

10. Pediatrics

On February 25, 2009, Alcon submitted a request for a partial pediatric waiver to this application.

The safety and effectiveness of the currently marketed Viagmox in infants below one year of age have not been established. The efficacy of the currently marketed Vigamox in treating bacterial

Division Director Review
Wiley A. Chambers M.D.
NDA 22-428
moxifloxacin hydrochloride ophthalmic solution, 0.5% as base

conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials.

There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested.

Per the DSI Clinical Inspection Summary dated 7/8/09, In general, Protocol C-04-38 appears to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the Clinical Investigator inspection of Dr. Watson is No Action Indicated (NAI). The preliminary classification of the Clinical Investigator inspection of Dr. Christensen is VAI. While regulatory violations occurred at this site, the primary safety and efficacy data from this site are considered reliable.

FINANCIAL DISCLOSURE

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided by Alcon for clinical studies C-04-38, C-04-40, and C-05-15 submitted in this application.

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for the new formulation of moxifloxacin ophthalmic solution. There are two investigators and two subinvestigators who participated in the phase 3 safety and efficacy trials who have disclosed financial ties to the sponsor.

Investigators with Financial Interests or Arrangements

Clinical Study	Investigators
(b) (6)	(b) (6)
C-04-40	None
C-05-15	None

There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The proprietary name (b) (4) was proposed for this application on May 29, 2009. The

Division Director Review
Wiley A. Chambers M.D.
NDA 22-428
moxifloxacin hydrochloride ophthalmic solution, 0.5% as base

Division of Medication Error Prevention and Analysis (DMEPA) was consulted in this review cycle. After discussion between Alcon and DMEPA regarding the acceptability of the submitted name, Alcon subsequently withdrew their request for the review of (b) (4) on August 25, 2009. DMEPA did not complete a formal review after the withdrawal of the (b) (4) name.

BIOSTATISTICS

In Study C-04-38, the primary efficacy endpoint of clinical cure rate of the MITT population at TOC (Day 7) visit Moxifloxacin AF Ophthalmic Solution is not superior over Vehicle. Clinical cure rate for Moxifloxacin AF is at 72.3% compared to 67.3% for Vehicle with a treatment difference of 4.8% (95% CI: -5.2%, 14.8%). Similar conclusions can be reached in the MBITT, MPP and PP population. It is only in the ITT population where Moxifloxacin AF is found superior over vehicle. However, The ITT population is not an acceptable primary analysis population because some patients may not necessarily have culture positive to be considered bacterial conjunctivitis. Superiority of Moxifloxacin AF over Vehicle cannot also be based on microbiological success since this variable is not a clinical endpoint and does not accurately reflect clinical benefit translated as complete resolution of signs and symptoms of bacterial conjunctivitis. Neither can superiority be based on clinical cure at EOT (Day 4) visit because this is a secondary endpoint. Testing for significance among secondary endpoints is only applicable if the primary hypothesis has been rejected.

In study C-04-40, the reviewer does not find the results of the non-inferiority trial interpretable due to the choice of the non-inferiority margin and does not in any way establish efficacy of Moxifloxacin AF Ophthalmic Solution.

12. Labeling

A formal labeling review is deferred until additional data is submitted to support the application.

13. Regulatory Action

NDA 22-428, moxifloxacin alternate formulation ophthalmic solution 0.5% should receive a Complete Response Letter and will not be approved for the treatment of bacterial conjunctivitis based on the information currently submitted in this application.

Wiley A. Chambers, MD
Acting Division Director

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

/s/

WILEY A CHAMBERS
10/07/2009

Cross-Discipline Team Leader Review

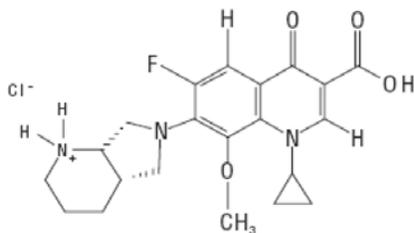
Date	October 5, 2009
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22-428
Applicant	Alcon Pharmaceuticals, Ltd.
Date of Submission	December 12, 2008
PDUFA Goal Date	October 15, 2009
Type of Application	505(b)(1)
Name	Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Indicated for the treatment of bacterial conjunctivitis
Recommended:	Not Recommended for Approval

1. Introduction

Throughout this review, Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base may alternately be referred to by various review disciplines as Moxifloxacin Alternate Formulation Ophthalmic Solution 0.5%, Moxifloxacin AF, or Vigamox AF.

Moxifloxacin is a fourth generation quinolone that was originally developed and approved for the treatment of various systemic bacterial infections. Alcon developed a topical ophthalmic formulation of moxifloxacin marketed as Vigamox for the treatment of bacterial conjunctivitis. The approved dosage and administration for Vigamox is one drop in the affected eye 3 times a day for 7 days. The current application is for an alternate formulation of moxifloxacin for the treatment of bacterial conjunctivitis. The alternate formulation contains a xanthan gum-^{(b) (4)} ^{(b) (4)} which is purported by Alcon ^{(b) (4)}. The objective of this formulation change is to maintain the same efficacy as the marketed Vigamox with only twice a day dosing.

Moxifloxacin hydrochloride was approved in Alcon's NDA 21-598 for Vigamox and is currently being marketed in the United States. Moxifloxacin hydrochloride is manufactured by Bayer AG in Wuppertal, Germany.



$C_{21}H_{24}FN_3O_4 \cdot HCl$

Mol Wt 437.9

Table 1 - Comparison of Compositions of Moxifloxacin AF and Vigamox

Component	% Composition	
	Moxifloxacin AF	Vigamox
Moxifloxacin hydrochloride	0.545 (b) (4)	same (b) (4)
Xanthan gum	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	(b) (4)
Boric acid	(b) (4)	(b) (4)
Sorbitol	(b) (4)	(b) (4)
Tyloxapol	(b) (4)	(b) (4)
Hydrochloric acid and/or sodium hydroxide	Adjust pH to 7.4	Adjust to pH 6.8
Purified water	(b) (4)	(b) (4)

The formulation of moxifloxacin AF used in the clinical studies is the same as the one intended for marketing.

2. Background

Alcon's proposed Phase 3 development program for moxifloxacin AF ophthalmic solution was discussed with the Agency in a Pre-IND/End of Phase 2 meeting on March 3, 2005. Alcon subsequently submitted Special Protocol Assessment requests for study C-04-38 and C-04-40, to which the Agency responded with comments on June 22, 2005. Comments on both studies were provided to Alcon. A Pre-NDA meeting package containing a summary of efficacy results from these studies was submitted to the Agency and comments were discussed at the Pre-NDA meeting on April 8, 2008.

Moxifloxacin AF is not marketed in any other country.

3. CMC

From the first and second CMC Reviews dated 8/24/09 and 10/5/09:

DRUG SUBSTANCE:

Moxifloxacin hydrochloride is a hydrochloride salt of moxifloxacin, fluoroquinolone carboxylic acid used as an antimicrobial agent. The applicant holds an approved NDA 21-598 on Vigamox, an ophthalmic solution containing the same drug substance. In NDA 21-598, Alcon referenced information from Bayer's NDA 21-085 for moxifloxacin hydrochloride tablets, for which a LoA was provided. The drug substance information provided in NDA 21-598 was found adequate in Dr. Su Tso's review dated April 14, 2003. No changes were observed in manufacturing and controls on drug substance in NDA 21-598 annual reports or supplements. Therefore, the drug substance information provided in NDA 21-598 is acceptable for the current application.

(b) (4)

DRUG PRODUCT:

Moxifloxacin alternative formulation ophthalmic solution, 0.5% (Moxifloxacin AF ophthalmic solution) is defined as a sterile, (b) (4) ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride, equivalent to 0.5% moxifloxacin. The proposed product is greenish yellow in color, which originates from the drug substance (DS). This product is developed using the same DS and for the same indication (topical treatment of bacterial conjunctivitis) as marketed Vigamox (moxifloxacin HCl ophthalmic solution) 0.5% as base (NDA 21-598). However, the proposed formulation has been modified with an intention (b) (4) with similar efficacy to Vigamox but with a less frequent dosing regimen from TID to BID.

The product will be packaged in a natural, low density polyethylene (LDPE) bottle with a

CDTL Review

William M. Boyd, M.D.

NDA 22-428

Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

polyethylene (LDPE) natural dispensing plug and a tan polypropylene (PP) closure.

No (b) (4) is used in the proposed formulation. As with the marketed Vigamox product, the applicant has stated that Moxifloxacin AF ophthalmic solution maintains adequate (b) (4) to meet USP (b) (4) effectiveness requirements in the absence of a (b) (4) agent (see Product Quality Micro Review, Section 6 this review).

Table 2b – Regulatory Specifications

(b) (4)



Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

All facilities were found acceptable for NDA 22-428 by Compliance as attached in EER at the end of the second CMC review.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology Toxicology Review finalized 7/14/09:

This product is a reformulation of Vigamox (b) (4). Both Moxifloxacin AF and Vigamox contain 0.5% moxifloxacin. Vigamox must be applied to the eye 3 times a day, but Moxifloxacin AF will be labeled for twice daily application.

Daily topical application of 0.5% Moxifloxacin AF to rabbits for up to one month was not associated with ocular inflammation, irritation, or toxicity. Higher concentrations of moxifloxacin (1%, 1.5%) in the same AF vehicle did not cause inflammation, but microscopic evaluation indicated signs of minor irritation in the lower conjunctiva and third eyelid. Ophthalmic examination (biomicroscopy/slit lamp, indirect ophthalmoscopy) did not reveal any changes associated with Moxifloxacin AF treatment at concentrations up to 1.5%. Moxifloxacin AF, 0.5%, did not impede wound healing in rabbits when applied following a keratectomy.

When administered systemically, moxifloxacin is widely distributed with tissue concentrations often exceeding those found in plasma. Approximately half of the dose is metabolized via glucuronide and sulfate conjugation. The remainder of the dose is excreted unchanged. Moxifloxacin is excreted in both urine (unchanged drug, glucuronide conjugate) and feces (unchanged drug, sulfate conjugate). Systemic availability of moxifloxacin was very low in human subjects when Moxifloxacin AF was applied to both eyes twice daily for 4 days, then once on Day 5 (C_{max} 0.977 ± 0.673 ng/ml; AUC 8.17 ± 5.31 ng·hr/ml).

The genotoxic profile of moxifloxacin is comparable to other fluoroquinolones. It was mutagenic in one of 5 bacterial strains used for the Ames test (TA 102) and clastogenic in a chromosome aberration assay using cultured cells. It did not induce unscheduled DNA synthesis *in vitro* and was negative in a mouse micronucleus test *in vivo*.

Moxifloxacin had no effect on fertility in rats at systemic doses far above those that can be achieved using a topical ophthalmic route. It was not teratogenic in rats and monkeys given oral doses far above the highest recommended total daily human ophthalmic dose.

Moxifloxacin AF appears reasonably safe to use as directed in the proposed product label. The pharmacologist has no objection to the approval of this NDA.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 7/15/09:

Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Moxifloxacin Alternative Formulation (AF; moxifloxacin hydrochloride ophthalmic solution) 0.5% is a sterile solution for topical ophthalmic use. Moxifloxacin hydrochloride is an 8-methoxy fluoroquinolone anti-infective and was initially developed as tablet and intravenous formulations. Moxifloxacin hydrochloride is approved in the U.S. as AVELOX for treatment of various bacterial infections, including acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated and complicated skin and skin structure infections, and complicated intra-abdominal infections. In addition, a topical ophthalmic formulation of moxifloxacin is marketed in the U.S. as VIGAMOX (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base, for the treatment of bacterial conjunctivitis. The approved dosage of VIGAMOX is one drop in the affected eye three times a day for seven days. Moxifloxacin AF is proposed for the treatment of bacterial conjunctivitis. The proposed dosage and route of administration for Moxifloxacin AF is as follows: instill one drop in the affected eye(s) two times daily for seven days.

The clinical development plan for Moxifloxacin AF Ophthalmic Solution included three clinical studies: one multiple-dose pharmacokinetic (PK) study in healthy adults (Study C-05-15), one Phase 3 superiority trial comparing Moxifloxacin AF Ophthalmic Solution to Moxifloxacin AF Ophthalmic Solution vehicle (Study C-04-38), and one Phase 3 comparative non-inferiority study of Moxifloxacin AF Ophthalmic Solution versus VIGAMOX (Study C-04-40). The extent of systemic exposure to moxifloxacin following topical ophthalmic administration of Moxifloxacin AF was evaluated in a double-masked, vehicle-controlled, parallel-group, multiple-dose pharmacokinetic (PK) study in healthy adults (Study C-05-15). The clinical pharmacology findings from this study are summarized as follows:

- Following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days, a mean peak plasma concentration of 0.977 ± 0.673 ng/mL (range: 0.267 to 3.19 ng/mL) was observed within approximately one hour.
- Moxifloxacin concentrations declined in a monophasic manner with terminal half-lives ranging from 7.6 to 27.3 hours (mean half life: 16.6 ± 5.5 hours) in healthy subjects.
- Steady-state following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% was achieved between 3 to 4 days. The estimated accumulation ratio was 2.5.
- C_{max} and AUC_{0-8} for moxifloxacin following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days were approximately 36% and 45%, respectively, of the C_{max} and AUC_{0-8} observed following TID dosing for 5 days with the previously approved moxifloxacin ophthalmic formulation VIGAMOX.
- Moxifloxacin C_{max} following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days is approximately 0.02% of that achieved with the oral formulation of moxifloxacin hydrochloride (C_{max} values: Moxifloxacin AF, 0.977 ± 0.88 ng/mL versus AVELOX, 4.5 ± 0.5 µg/mL). These findings suggest a wide margin of safety for Moxifloxacin AF ophthalmic solution.

Based on the assessment of systemic exposure information for Moxifloxacin AF from a multiple-dose PK study in healthy adult male and female volunteers, the regulatory requirement for submission of in vivo bioavailability data has been adequately addressed.

6. Sterility Assurance

From the Product Quality Microbiology review completed 9/29/09:

Container-Closure and Package Integrity

The integrity of the container/closure system for stability samples was demonstrated by successful sterility testing of each of the three primary stability lots of each of the 1ml and 3ml fill sizes (lot numbers SLN-0363, SLN-0365, SLN-0366, SLN-0368, SLN-0369, SLN-0371).

In addition, microbial ingress tests were conducted. For each of three validation runs, the challenged units were negative for growth. Positive controls were confirmed for E. coli growth, and negative controls showed no growth. Acceptable TSB growth promotion testing (< 100 CFU/ml E. coli) was performed. Plate counts were used to confirm the pre- and post-exposure microbial challenge (pre = 8.5 to 9.7 x 10⁷ CFU/ml; post = 7.5 to 9.2 x 10⁷ CFU/ml).

(b) (4) Effectiveness

The drug product does not contain any traditional (b) (4) and the Applicant describes it as (b) (4). (b) (4) effectiveness testing was conducted on the six stability batches (3 lots of each fill size - lot numbers SLN-0363, SLN-0365, SLN-0366, SLN-0368, SLN-0369, SLN-0371).

Test data indicated that the drug product met or exceeded the USP <51> acceptance criteria for antimicrobial effectiveness. For the six lots tested at the three time periods, the drug product exhibited the following ranges for the reduction of organism counts:

Organism	Log10 unit reduction of microorganisms after		
	7 days	14 days	28 days
S. aureus (ATCC 65338)	4.8-5.4	4.8-5.4	4.8-5.4
P. aeruginosa (ATCC 9027)	4.6-5.4	4.6-5.4	4.6-5.4
E. coli (ATCC 8739)	4.9-5.4	4.9-5.4	4.9-5.4
C. albicans (ATCC 10231)	1.3-2.8	2.3-4.2	4.1-5.5
A. niger (ATCC 16404)	0.8-1.7	2.1-4.4	3.9-4.4

These results indicate the (b) (4) - (b) (4) nature of the drug product formulation. Such product development study results mitigate the lack of a routine release assay for (b) (4) effectiveness.

The Product Quality Microbiology Reviewer has identified two issues to be addressed by the applicant.

1. The specification for bacterial endotoxin (NMT (b) (4)) while similar to some other Alcon topical ophthalmic drug products containing xanthan gum, is higher than the expected limit of (b) (4) for such drug products. The applicant is advised, as part of the product's continual process improvement life cycle, to establish a program to lower the acceptance criteria to NMT (b) (4)



7. Clinical/Statistical - Efficacy

From the original Medical Officer Review finalized 8/12/2009:

This application contained two safety and efficacy trials to support the approval of moxifloxacin AF for the treatment of bacterial conjunctivitis. Study C-04-38 was a two-arm superiority trial comparing moxifloxacin to vehicle; C-04-40 was a non-inferiority trial which compared the new formulation to the currently marketed Vigamox. Study C-04-38 was considered to be the most crucial for determining the efficacy of this product since the non-inferiority margin for study C-04-40 essentially requires the new formulation to be superior to Vigamox.

The primary clinical efficacy variable in Study C-04-38 was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection (bulbar conjunctival injection and conjunctival discharge/exudate). Clinical cure was attained when the sum of the two cardinal ocular signs was zero (i.e., normal or absent) at Day 7. The primary microbiological efficacy variable was the bacterial eradication rate at the Exit visit.

The primary clinical efficacy variable in Study C-04-40 was clinical cure. Clinical cure was achieved when the sum of the ratings for the cardinal ocular signs (bulbar conjunctival injection and conjunctival discharge/exudate) was zero (i.e. normal or absent) at the TOC (test of cure) visit (Day 7). The primary microbiological efficacy variable was microbiological success. Microbiological success was achieved when the pre-therapy pathogens were eradicated at TOC.

Analyses of Endpoints

Study C-04-38

	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	129 (72.5%)	128 (72.3%)	105 (75%)
Vehicle	113 (67.7%)	111 (67.3%)	88 (66.2%)
p-value	0.3295	0.3097	0.1089

	Microbiological Success at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	150 (84.3%)	149 (84.2%)	115 (82.7%)
Vehicle	110 (65.9%)	109 (66.1%)	90 (67.7%)
p-value	< 0.0001	0.0001	0.0039

The Agency informed Alcon during development that the Microbiological Intent-to-Treat¹ (MBITT) population would be used for the efficacy evaluation. Study C-04-38 failed to demonstrate efficacy for clinical cure at day 7. The Modified Intent-to-Treat² (MITT) and Modified Per Protocol³ (MPP) population results are consistent with the MBITT population.

Study C-04-40

	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	152 (80.4%)	150 (80.2%)	103 (84.4%)
Vigamox	163 (84.5%)	161 (84.3%)	108 (85.7%)
p-value	0.30	0.3	0.78
Delta	-4.1	-4.1	-1.3
LCL	-11.65	-11.78	-10.16
UCL	3.62	3.62	7.59

	Microbiological Success at Day 7		
	MBITT	MITT	MPP

¹ Microbiological Intent-to-Treat (MBITT): All patients who received drug, had at least one on-therapy visit and were pathogen positive for bacteria on Day 1.

² Modified Intent-to-Treat (MITT): All patients who received drug, had at least one on therapy visit, met pre-randomization inclusion and exclusion criteria and were pathogen positive for bacteria on Day 1.

³ Modified Per Protocol (MPP): All patients who received drug, met pre-randomization inclusion and exclusion criteria, had baseline and test of cure (or exit if the patient exited from the study early) visits and were pathogen positive for bacteria on Day 1.

Moxifloxacin AF	165 (87.3%)	163 (87.2%)	112 (92.6%)
Vigamox	173 (89.6%)	171 (89.5%)	115 (92%)
p-value	0.48	0.47	0.87
Delta	-2.3	-2.3	0.6
LCL	-8.74	-8.8	-6.11
UCL	4.07	4.1	7.23

Alcon evaluated the data based on a non-inferiority margin of 15%. The Division does not agree that this is a justifiable margin based on available clinical trial data. Initial review of the available efficacy data suggests that an acceptable non-inferiority margin for topical anti-infectives may be in the range of 2%-6%. The results of this trial suggest that Moxifloxacin AF is inferior to Vigamox for both clinical cure and microbiological success.

Additionally, the dosing regimen used in this trial for Vigamox is inconsistent with the regimen use in the approval for this product. The clinical trials conducted to establish the efficacy of Vigamox were conducted with the drug dosed for 4 days. Clinical cure rates at the end-of-therapy visit (day5) ranged from 66-69% and 83-87% at test of cure (day 7). In the current study (C-04-40) Vigamox is dosed for only 3 days in the comparator arm. This is not the optimum dosing frequency and is not the regimen used in the clinical trials to establish efficacy. The clinical cure rate is 58% at the end-of-therapy (day 4) and approximately 84-85% at the test-of-cure visit (day 7).

Clinical Microbiology Review

From the Clinical Microbiology Review finalized 8/12/09:

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* (eradication 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 the following two tables.

Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Table 7a -Eradication Rate of Pre-therapy Pathogens by Moxifloxacin AF Ophthalmic Solution

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

E=number of isolates eradicated in successfully treated patients

P=number of isolates persisting in failed patients

%= Eradication Rate

Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Table 7b - Eradication Rates for Conjunctivitis Isolates Treated with Moxifloxacin AF 0.5%

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

^aTotal # 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.

^bIncludes isolates from only Moxi AF treated patients in C-04-38 and C-04-40

^cIncludes 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. 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).

Efficacy Summary Statement

The two clinical trials submitted in this NDA for approval of moxifloxacin AF fail to establish the efficacy for this product in the treatment of bacterial conjunctivitis. Study C-04-38 failed its pre-specified primary efficacy endpoint of clinical cure at day 7; however, microbiological eradication was demonstrated at this timepoint.

Study C-04-40 was not supportive of the efficacy because the non-inferiority margin essentially requires the new formulation to be superior to the currently marketed Vigamox based on the one placebo controlled clinical trial for Vigamox. In addition, the duration of dosing as well as the time point at which efficacy is measured differed between the trial used to establish the efficacy of Vigamox and the current trial. This makes any comparison between the two problematic as a margin will likely differ based on varying these two factors.

8. Safety

From the Medical Officer Review finalized 8/12/2009:

Both Study C-04-38 and Study C-04-40 were used in the safety analysis. Study C-05-15, a multiple-dose, double-masked, randomized, vehicle -controlled, parallel-group pharmacokinetic study in 30 subjects was also used in the safety analysis.

A total of 697 patients were exposed to moxifloxacin AF during development.

Table 8a - Overview of Exposure to Study Drug by Protocol

Protocol Number	Safety N	Moxifloxacin AF	Vigamox	Vehicle
C-04-38	661	331		330
C-04-40	695	346	349	
C-05-15	30	20		10

The age distribution of the patients exposed to moxifloxacin during development is as follows:

Table 8b - Exposure to Study Drug by Age Group

Age group	Number exposed
28 days to 23 months	68
2 to 11 years	143
12 to 17 years	38
18 to 64 years	399
65 years or older	39

The majority (85-97%) of patients in each age group were exposed to moxifloxacin AF for 3 days with another 2-8% exposed to a total of 4 days of drug.

Table 8c – Discontinuations in C-04-38 and C-04-40

Reason for discontinuation	C-04-38		C-04-40	
	Moxifloxacin AF	Vehicle	Moxifloxacin AF	Vigamox
Adverse Event	5	5	3	1
Lost to follow-Up	3	6	24	25
Decision Unrelated to an Adverse Event	5	5	2	2
Noncompliance	1	8	0	1
Treatment Failure	7	32	7	13
Other	1	4	0	0

Tables of the adverse events associated with the discontinuations are presented below. Based on the Medical Officer’s review of the Case Report Forms, it does not appear that the other discontinuations were due to adverse events. The “lost to follow-up” is unusually high for a one week study.

Table 8d - Adverse Events Associated with Discontinuation – Study C-04-38

Patient	Age	Sex	Treatment	Onset day	Adverse event
1720	48	F	Moxifloxacin AF	1	Foreign body sensation, increased lacrimation, conjunctival disorder
2005	32	M	Moxifloxacin AF	2	gonorrhea
1314	19	F	Moxifloxacin AF	2	Streptococcal pharyngitis
2218	1	M	Moxifloxacin AF	5	Sinusitis
102	15	M	Moxifloxacin AF	3	Conjunctivitis
405	1	M	Vehicle	2	Otitis Media
1312	3	M	Vehicle	4	Otitis media
2126	2	M	Vehicle	1	Periorbital cellulitis
926	42	F	Vehicle	5	conjunctivitis
104	41	M	Vehicle	4	Uveitis

Table 8e - Adverse Events Associated with Discontinuation – Study C-04-40

Patient	Age	Sex	Treatment	Onset day	Adverse event
3413	21	M	Moxifloxacin AF	2	Conjunctival edema, eyelid edema, ocular hyperemia
2422	41	M	Moxifloxacin AF	6	Conjunctival ulcer
4007	9	M	Moxifloxacin AF	1	Rhinitis, corneal opacity, punctuate keratitis, nasal congestion, pyrexia
3408	24	M	Vigamox	3	Conjunctival edema, eye pruritus, eyelid edema

Table 8f - Common Adverse Events (rate ≥ 1%) – Safety Population – Study C-04-38

Adverse Event	Moxifloxacin AF N=331		Vehicle N=330	
	N	%	N	%
<i>Eye disorders</i>				
Conjunctivitis	5	1.5	5	1.5
<i>Infections and infestations</i>				
Upper respiratory tract infection	6	1.8	5	1.5
Otitis media	2	0.6	6	1.8
<i>Nervous system disorders</i>				
Headache	0	0	6	1.8
<i>General disorders and administration site conditions</i>				
Pyrexia	2	0.6	4	1.2

Table 8 g - Common Adverse Events (rate ≥ 1%) – Safety Population – Study C-04-40

Adverse Event	Moxifloxacin AF N=346		Vigamox N=349	
	N	%	N	%
<i>Eye disorders</i>				
Eye irritation	8	2.3	5	1.4
Eye pain	8	2.3	7	2.0
Conjunctivitis	5	1.4	2	0.6
Punctuate keratitis	5	1.4	5	1.4
Eye pruritus	1	0.3	5	1.4
<i>General disorders and administration site conditions</i>				
Pyrexia	7	2.0	7	2.0

POSTMARKETING EXPERIENCE

Moxifloxacin AF is not marketed in any country. Moxifloxacin hydrochloride ophthalmic solution, 0.5% base is approved in more than 50 countries. It was approved in the U.S. in 2003. Alcon has received 471 spontaneous adverse event reports worldwide associated with moxifloxacin. Thirty-five (35) were considered serious. The spontaneous postmarketing reports for moxifloxacin are consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with moxifloxacin.

Safety Summary Statement

There are no new safety concerns raised in this NDA submission concerning the use of moxifloxacin for the treatment of bacterial conjunctivitis. The adverse events reported during the phase 3 studies were similar to those listed in the package insert of the currently marketed fluoroquinolone ophthalmic solutions. No clinically significant differences were found between moxifloxacin AF and the active control Vigamox in the frequency or type of adverse events.

The benefit of moxifloxacin in the treatment of bacterial conjunctivitis has not been demonstrated in this NDA application. The risk for using this drug is mild and is consistent with the currently marketed Vigamox. However, the risk/benefit profile has not been established.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for moxifloxacin hydrochloride ophthalmic solution 0.5%.

10. Pediatrics

On February 25, 2009, Alcon submitted a request for a partial pediatric waiver to this application.

The safety and effectiveness of the currently marketed Viagmox in infants below one year of age have not been established. The efficacy of the currently marketed Vigamox in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials.

There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested.

Per the DSI Clinical Inspection Summary dated 7/8/09, In general, Protocol C-04-38 appears to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the Clinical Investigator inspection of Dr. Watson is No Action Indicated (NAI).

The preliminary classification of the Clinical Investigator inspection of Dr. Christensen is VAI. While regulatory violations occurred at this site, the primary safety and efficacy data from this site are considered reliable.

FINANCIAL DISCLOSURE

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided by Alcon for clinical studies C-04-38, C-04-40, and C-05-15 submitted in this application.

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for moxifloxacin AF ophthalmic solution. There are two investigators and two subinvestigators who participated in the phase 3 safety and efficacy trials who have disclosed financial ties to the sponsor.

Investigators with Financial Interests or Arrangements

Clinical Study	Investigators
[REDACTED]	[REDACTED] (b) (6)
C-04-40	None
C-05-15	None

There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The proprietary name [REDACTED] (b) (4) [REDACTED] (b) (4) was proposed for this application on May 29, 2009. The Division of Medication Error Prevention and Analysis (DMEPA) was consulted in this review cycle. After discussion between Alcon and DMEPA regarding the acceptability of the submitted name, Alcon subsequently withdrew their request for the review of [REDACTED] (b) (4) [REDACTED] (b) (4) on August 25, 2009. DMEPA did not complete a formal review after the withdrawal of the [REDACTED] (b) (4) [REDACTED] (b) (4) name.

In an email dated July 30, 2009, the DMEPA Safety Evaluator provided the following comments to the Review Division regarding [REDACTED] (b) (4) [REDACTED] (b) (4)

During our preliminary assessment of the proposed proprietary name [REDACTED] (b) (4) [REDACTED] (b) (4) we noted that the Applicant has proposed [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

CDTL Review
William M. Boyd, M.D.
NDA 22-428

Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base



In an email dated August 12, 2009, the Review Division provided the following comments to the DMEPA Safety Evaluator regarding (b) (4) (b) (4)



We consider the product currently proposed with the name (b) (4) (b) (4) to be a different product from Vigamox. At the present time, it appears to be less effective than Vigamox, although we cannot determine whether it is less effective because of something in the revised formulation or because it was dosed less frequently.

There are clinical consequences of mixing these products because it appears that (b) (4) (b) (4) is less effective. We are not likely to approve the product unless it is at least as effective as Vigamox.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) was not consulted in this review cycle.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 9/16/09:

Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

There were two clinical studies submitted in support for Moxifloxacin AF in the treatment of bacterial conjunctivitis. The first study, C-04-38, is a superiority study of Moxifloxacin AF over vehicle while the second study, C-04-40 is a noninferiority study of Moxifloxacin AF compared to VIGAMOX.

In Study C-04-38, the primary efficacy endpoint of clinical cure rate of the MITT population at TOC (Day 7) visit Moxifloxacin AF Ophthalmic Solution is not superior over Vehicle. Clinical cure rate for Moxifloxacin AF is at 72.3% compared to 67.3% for Vehicle with a treatment difference of 4.8% (95% CI: -5.2%, 14.8%). Similar conclusions can be reached in the MBITT, MPP and PP population. It is only in the ITT population where Moxifloxacin AF is found superior over vehicle. However, The ITT population is not an acceptable primary analysis population because some patients may not necessarily have culture positive to be considered bacterial conjunctivitis. Superiority of Moxifloxacin AF over Vehicle cannot also be based on microbiological success since this variable is not a clinical endpoint and does not accurately reflect clinical benefit translated as complete resolution of signs and symptoms of bacterial conjunctivitis. Neither can superiority be based on clinical cure at EOT (Day 4) visit because this is a secondary endpoint. Testing for significance among secondary endpoints is only applicable if the primary hypothesis has been rejected.

In study C-04-40, the reviewer does not find the results of the non-inferiority trial interpretable due to the choice of the non-inferiority margin and does not in any way establish efficacy of Moxifloxacin AF Ophthalmic Solution.

12. Labeling

A formal labeling review is deferred until additional data is submitted to support the application for Moxifloxacin AF.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

It is recommended from a clinical prospective that NDA 22-428, Moxifloxacin Alternate Formulation Ophthalmic Solution 0.5% receive a Complete Response Letter and not be approved for the treatment of bacterial conjunctivitis.

RISK BENEFIT ASSESSMENT:

The two clinical trials submitted in this NDA for approval of moxifloxacin AF fail to establish the efficacy for this product in the treatment of bacterial conjunctivitis.

There are no new safety concerns raised in this NDA submission concerning the use of moxifloxacin for the treatment of bacterial conjunctivitis. The adverse events reported during the phase 3 studies were similar to those listed in the package insert of the currently marketed

CDTL Review
William M. Boyd, M.D.
NDA 22-428

Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

fluoroquinolone ophthalmic solutions. No clinically significant differences were found between moxifloxacin AF and the active control Vigamox in the frequency or type of adverse events.

Pharmacology/Toxicology, Clinical Microbiology, CMC, and Clinical Pharmacology have recommended approval for this application.

Clinical and Biostatistics do not recommend approval.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

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

There are no recommended Postmarketing Requirements.

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

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

/s/

WILLIAM M BOYD
10/05/2009

WILEY A CHAMBERS
10/07/2009

CLINICAL REVIEW

Application Type	N
Application Number(s)	NDA22-428
Priority or Standard	Standard
Submit Date(s)	December 12, 2008
Received Date(s)	December 15, 2008
PDUFA Goal Date	October 15, 2009
Reviewer Name(s)	Jennifer D. Harris, M.D.
Review Completion Date	July 16, 2009
Established Name	moxifloxacin hydrochloride ophthalmic solution
(Proposed) Trade Name	(b) (4) (b) (4)
Therapeutic Class	quinolone
Applicant	Alcon Pharmaceuticals
Formulation(s)	Ophthalmic solution
Dosing Regimen	One (1) drop in the affected eye (s) twice a day
Indication(s)	Bacterial Conjunctivitis
Intended Population(s)	Patients ages 1 and older with bacterial conjunctivitis

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	4
1.1 Recommendation on Regulatory Action	4
1.2 Risk Benefit Assessment.....	4
1.3 Recommendations for Postmarket Risk Management Activities	4
1.4 Recommendations for Postmarket Studies/Clinical Trials.....	5
2 INTRODUCTION AND REGULATORY BACKGROUND	5
2.1 Product Information	5
2.2 Tables of Currently Available Treatments for Proposed Indications	5
2.3 Availability of Proposed Active Ingredient in the United States	5
2.4 Important Safety Issues With Consideration to Related Drugs.....	6
2.5 Summary of Presubmission Regulatory Activity Related to Submission	6
2.6 Other Relevant Background Information.....	6
3 ETHICS AND GOOD CLINICAL PRACTICES.....	6
3.1 Submission Quality and Integrity	6
3.2 Compliance with Good Clinical Practices	6
3.3 Financial Disclosures	7
4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	7
4.1 Chemistry Manufacturing and Controls	7
4.2 Clinical Microbiology.....	8
4.3 Preclinical Pharmacology/Toxicology	8
4.4 Clinical Pharmacology.....	8
4.4.1 Mechanism of Action	9
4.4.2 Pharmacodynamics	9
4.4.3 Pharmacokinetics	9
5 SOURCES OF CLINICAL DATA.....	10
5.1 Tables of Studies/Clinical Trials.....	10
5.2 Review Strategy.....	10
5.3 Discussion of Individual Studies/Clinical Trials.....	11
6 REVIEW OF EFFICACY	20
Efficacy Summary	20
6.1 Indication	20
6.1.1 Methods.....	20
6.1.2 Demographics	20
6.1.3 Subject Disposition	22
6.1.4 Analysis of Primary Endpoint(s).....	23
6.1.5 Analysis of Secondary Endpoints(s)	26
6.1.6 Other Endpoints	26
6.1.7 Subpopulations.....	27
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.....	28
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects	29
6.1.10 Additional Efficacy Issues/Analyses.....	30
7 REVIEW OF SAFETY	32
Safety Summary.....	32
7.1 Methods	32

Clinical Review

{Jennifer D. Harris, MD}

{NDA 22-428}

(b)(4) (moxifloxacin AF)

7.1.1 Studies/Clinical Trials Used to Evaluate Safety.....	32
7.1.2 Categorization of Adverse Events.....	32
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	33
7.2 Adequacy of Safety Assessments.....	33
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	33
7.2.2 Explorations for Dose Response.....	33
7.2.3 Special Animal and/or In Vitro Testing.....	34
7.2.4 Routine Clinical Testing.....	34
7.2.5 Metabolic, Clearance, and Interaction Workup.....	34
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	34
7.3 Major Safety Results.....	34
7.3.1 Deaths.....	34
7.3.2 Nonfatal Serious Adverse Events.....	34
7.3.3 Dropouts and/or Discontinuations.....	34
7.3.4 Significant Adverse Events.....	36
7.3.5 Submission Specific Primary Safety Concerns.....	36
7.4 Supportive Safety Results.....	36
7.4.1 Common Adverse Events.....	36
7.4.2 Laboratory Findings.....	37
7.4.3 Vital Signs.....	37
7.4.4 Electrocardiograms (ECGs).....	38
7.4.5 Special Safety Studies/Clinical Trials.....	38
7.4.6 Immunogenicity.....	38
7.5 Other Safety Explorations.....	38
7.5.1 Dose Dependency for Adverse Events.....	38
7.5.2 Time Dependency for Adverse Events.....	38
7.5.3 Drug-Demographic Interactions.....	38
7.5.4 Drug-Disease Interactions.....	38
7.5.5 Drug-Drug Interactions.....	38
7.6 Additional Safety Evaluations.....	39
7.6.1 Human Carcinogenicity.....	39
7.6.2 Human Reproduction and Pregnancy Data.....	39
7.6.3 Pediatrics and Assessment of Effects on Growth.....	39
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	39
7.7 Additional Submissions.....	39
8 POSTMARKET EXPERIENCE.....	40
9 APPENDICES.....	41
9.1 Literature Review/References.....	41
9.2 Labeling Recommendations.....	41
9.3 Advisory Committee Meeting.....	41

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The submitted studies do not show that this alternate formulation of moxifloxacin has efficacy for the treatment of bacterial conjunctivitis. Approval of the application is not recommended.

1.2 Risk Benefit Assessment

The two clinical trials submitted in this NDA for approval of moxifloxacin AF fail to establish the efficacy for this product in the treatment of bacterial conjunctivitis. Study C-04-38 failed its pre-specified primary efficacy endpoint of clinical cure at day 7; however, microbiological eradication was demonstrated at this timepoint. The failure of clinical cure at day 7 could have been due to poor trial design as opposed to the drug product itself. These design factors may have included the duration of treatment and the time point at which the efficacy endpoint was measured. Based on the fact that bacterial conjunctivitis is a self limited disease and the fact that the placebo contains a preservative that is effective in eradicating bacterial organisms, the timing of dosing and efficacy measurements become critical. While this may be scientifically plausible, this is only speculation and can not be determined by the available data.

Study C-04-40 was only used as supportive evidence of efficacy and safety because of the design of the trial. This study is a non-inferiority study that compared moxifloxacin AF to the currently marketed Vigamox. A non-inferiority margin has not been established for this product. There is currently only one placebo controlled clinical trial for Vigamox. In addition, the duration of dosing as well as the time point at which efficacy is measured differed between the trial used to establish the efficacy of Vigamox and the current trial which makes any comparison between the two problematic as a margin will likely differ based on varying these two factors. Determination of a margin in the future will need to take these factors into account.

There are no new safety concerns raised in this NDA submission concerning the use of moxifloxacin for the treatment of bacterial conjunctivitis. The adverse events reported during the phase 3 studies were similar to those listed in the package insert of the currently marketed fluoroquinolone ophthalmic solutions. No clinically significant differences were found between moxifloxacin AF and the active control Vigamox in the frequency or type of adverse events.

The benefit of moxifloxacin in the treatment of bacterial conjunctivitis has not been demonstrated in this NDA application. The risk for using this drug is mild and is consistent with the currently marketed Vigamox. However, the risk/benefit profile has not been established.

1.3 Recommendations for Postmarket Risk Management Activities

N/A – approval of Moxifloxacin AF is not recommended.

1.4 Recommendations for Postmarket Studies/Clinical Trials

N/A – approval of Moxifloxacin AF is not recommended.

2 Introduction and Regulatory Background

Moxifloxacin is a fourth generation quinolone that was originally developed and approved for the treatment of various systemic bacterial infections. Alcon developed a topical ophthalmic formulation of moxifloxacin marketed as Vigamox for the treatment of bacterial conjunctivitis. The approved dosage and administration for Vigamox is one drop in the affected eye 3 times a day for 7 days. The current application is for an alternate formulation of moxifloxacin for the treatment of bacterial conjunctivitis. The alternate formulation contains a xanthan gum- (b) (4) (b) (4) which is expected to (b) (4). The objective of this change is to maintain the same efficacy as Vigamox with only twice a day dosing.

2.1 Product Information

Established Name: moxifloxacin hydrochloride ophthalmic solution 0.5%
Proposed Trade Name: (b) (4) (b) (4)
Chemical Class: new formulation
Pharmacological Class: quinolone
Indication: treatment of bacterial conjunctivitis

Dosing Regimen: One drop in the affected eye(s) two times a day for seven days
Age Groups: adults and children over the age of one month

2.2 Tables of Currently Available Treatments for Proposed Indications

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

2.3 Availability of Proposed Active Ingredient in the United States

Moxifloxacin hydrochloride was approved in Alcon's NDA 21-598 for Vigamox and is currently being marketed in the United States. Moxifloxacin hydrochloride is manufactured by Bayer AG in Wuppertal, Germany.

2.4 Important Safety Issues With Consideration to Related Drugs

Ophthalmic anti-infectives are generally well tolerated and effective for bacterial conjunctivitis. There are no specific issues which warrant special attention.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Alcon's proposed phase 3 development program for moxifloxacin AF ophthalmic solution was discussed with the Agency in a pre-IND/end of phase 2 meeting on March 3, 2005. Alcon subsequently submitted Special Protocol Assessment requests for study C-04-38 and C-04-40, to which the Agency responded with comments on June 22, 2005. Comments on both studies were provided to the sponsor. A pre-NDA meeting package containing a summary of efficacy results from these studies was submitted to the Agency and comments were discussed at the pre-NDA meeting on April 8, 2008.

2.6 Other Relevant Background Information

Moxifloxacin AF is not marketed in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

Clinical investigator (CI) inspections were conducted for study C-04-38 only. The sites requested for inspection were two of five centers that all appeared to be operating under an umbrella site management organization called (b)(4). All five of these sites also utilized the same ophthalmology group as sub-investigators to conduct the examinations. The sum of enrollment at these five centers (>110 subjects) represented approximately 17% of the subjects enrolled in this study. The two sites (Dr. Watson and Dr. Christensen) were among those with the highest enrollment and had no prior inspection history.

Per DSI assessment, study C-04-38 appears to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the Clinical Investigator inspection of Dr. Watson is No Action Indicated (NAI).

The preliminary classification of the Clinical Investigator inspection of Dr. Christensen is VAI. The violations at this site involved discrepancies between (b) (4) microbiology reports and microbiology findings recorded in line listings. Errors present in microbiology line listings do not represent a regulatory violation attributable to the clinical investigator; rather they appear to be errors that occurred in some way with transfer of data between (b) (4) and the Applicant or in generation of line listings by the Applicant. While regulatory violations occurred at this site, the primary safety and efficacy data from this site are considered reliable.

3.3 Financial Disclosures

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for moxifloxacin AF ophthalmic solution. There are two investigators and two subinvestigators who participated in the phase 3 safety and efficacy trials who have disclosed financial ties to the sponsor.

Investigators with financial Interests or Arrangements

Clinical Study	Investigators
	(b) (6)
C-04-40	None
C-05-15	None

A review of these arrangements do not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Moxifloxacin Alternative Formulation Ophthalmic solution, 0.5% is a sterile, stable, (b) (4) ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride. The product was developed using the same active ingredient and for the same indication (topical treatment of bacterial conjunctivitis) as Vigamox. The modified formulation contains a xanthan gum (b) (4)

Composition of Moxifloxacin AF Ophthalmic Solution

Component	Percent w/v	Purpose
Moxifloxacin hydrochloride	0.545	Active
Xanthan gum	(b) (4)	(b) (4)
Sodium chloride		
Boric acid		
Sorbitol		
Tyloxapol		
Hydrochloric acid and/or sodium hydroxide	Adjust pH to 7.4	pH adjuster
Purified water	(b) (4)	(b) (4)

Comparison of Compositions of Moxifloxacin AF and Vigamox

Component	% Composition	
	Moxifloxacin AF	Vigamox
Moxifloxacin hydrochloride	0.545	same
Xanthan gum	(b) (4)	(b) (4)
Sodium chloride		
Boric acid		
Sorbitol		
Tyloxapol		
Hydrochloric acid and/or sodium hydroxide	Adjust pH to 7.4	Adjust to pH 6.8
Purified water	(b) (4)	(b) (4)

The formulation of Moxifloxacin AF used in the clinical studies are the same as the one intended for marketing.

4.2 Clinical Microbiology

See section 6.1.10.

4.3 Preclinical Pharmacology/Toxicology

Ocular PK studies in rabbits showed that the concentration of moxifloxacin in tears fell more rapidly following application of Vigamox than following application of Moxifloxacin AF.

Additionally, the levels of moxifloxacin in the aqueous humor of rabbits was higher after application of Moxifloxacin AF compared to Vigamox.

Moxifloxacin AF was well tolerated by rabbits when applied to the eyes several times daily for one month. Neither ocular irritation nor toxicity were observed with the formulation and concentration of active ingredient to be marketed. There were microscopic signs of slight irritation at higher moxifloxacin concentrations >1% (same vehicle as Moxifloxacin AF), but no inflammation.

Moxifloxacin AF appears reasonably safe to use as directed. This product caused neither ocular irritation nor toxicity when applied to rabbit eyes several times daily for one month.

See Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for moxifloxacin was previously submitted and evaluated as part of the Vigamox NDA (NDA 21-598). The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

4.4.2 Pharmacodynamics

See biopharmaceutics review.

4.4.3 Pharmacokinetics

See biopharmaceutics review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
C-05-15 Multiple dose topical ocular PK/safety study	Multiple-dose, double-masked, randomized, vehicle – controlled, parallel-group	Healthy adult male and female volunteers	Moxifloxacin AF ophthalmic solution Vehicle	1 drop BID OU 1 drop BID OU	4 days with final dose on morning of Day 5	30
C-04-38 Safety/efficacy study	Prospective, randomized, vehicle-controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution Vehicle	1 drop BID OU 1 drop BID OU	3 days	661 (345 culture positive diagnosed eye)
C-04-40 Safety/efficacy study	Prospective, randomized, active-controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution <u>and</u> Vehicle Vigamox	1 drop BID OU <u>and</u> 1 drop BID OU 1 drop TID OU	3 days	695 (382 culture positive diagnosed eye)

5.2 Review Strategy

This application contained two safety and efficacy trials to support the approval of moxifloxacin AF for the treatment of bacterial conjunctivitis. Study C-04-38 was a two-arm superiority trial comparing moxifloxacin to vehicle; C-04-40 was a non-inferiority trial which compared the new formulation to the currently marketed Vigamox. Since a non-inferiority margin has not been established for Vigamox, C-04-40 was not viewed as a study that could be used to establish the efficacy of moxifloxacin AF. Study C-04-38 was considered to be the most crucial for determining the efficacy of this product while the results from C-04-40 were considered as supportive evidence. Both studies were used in the safety analysis.

5.3 Discussion of Individual Studies/Clinical Trials

Study #1 C-04-38

Title: An Evaluation of the Safety and Efficacy of Moxifloxacin AF Ophthalmic Solution 0.5% for the Treatment of Bacterial Conjunctivitis in the USA

Study Design

This study was a prospective, multi-center (32 sites), double-masked, parallel group, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of topical ocular moxifloxacin AF ophthalmic solution compared to vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. Approximately 600 patients with a clinical diagnosis of bacterial conjunctivitis were targeted for enrollment to achieve at least 300 (150 on moxifloxacin AF ophthalmic solution and 150 on vehicle) bacterial pathogen positive patients. Enrollment in the study included patients one month of age or older and excluded all considerations of race, occupation, socioeconomic status, or gender.

On Day 1, eligible patients who met all inclusion criteria were randomized into one of two treatment groups, moxifloxacin AF ophthalmic solution or vehicle. Both groups were dosed with one drop two times per day. Treatment continued for 3 days with a test-of-cure follow-up visit at 60 to 96 hours after the last dose of medication.

Study Plan

Parameters	Day 1 Screening /baseline	Day 3 (-1)	Day 4 (EOT) 12-48 Hrs post-last dose	Ophthalmologist Exit Visit (TOC)^a 60-96 Hrs post- last dose
Screen for inclusion/exclusion criteria	X			
Informed Consent	X			
Urine Pregnancy Test ^b	X			X
General Information: Medical History	X			
Vaccination Information (Patients ≤ 12 yrs)	X			
Changes in concomitant medication or general health		X	X	X
Patients Rate Ocular Symptoms	X	X	X	X
Visual Acuity	X	X	X	X
Investigator Rates Ocular Signs	X	X	X	X
Evaluation of Cornea and Iris/Anterior Chamber	X	X	X	X
Collect Ocular Microbiological Specimens ^c	X			X
Fundus Exam of Posterior Pole ^d	X		X	X
First Dose of Study Medication (in-office)	X			
Dispense Study Medication ^e	X	X		
Record Adverse Events	X ^f	X	X	X
Collect Study Medication ^e		X	X	X
Complete Exit Form ^a				X

^a At any time a patient exits from the study.

^b For women of child-bearing potential, before instillation of drug and at exit from the study.

^c At Day 1 and at any time a patient exits from the study. The specimens must have been collected prior to the fundus exam.

^d All fundus examinations conducted by Ophthalmologists were to be dilated. Those conducted by non-ophthalmologists were to be undilated.

^e As needed.

^f After dosing.

Inclusion Criteria

Study participants included patients one month of age or older of either sex and any race with a diagnosis of bacterial conjunctivitis based on clinical observation. All patients had a rating of ≥ 1 (mild) on a scale of 0 to 3 (absent to severe) for bulbar conjunctival injection and conjunctival discharge/exudate at the Day 1 visit. Patients ≥ 3 years of age must have had visual acuity correctable to 0.6 logMAR or better in both eyes. Visual acuity measurements for children < 3

years of age were conducted at the discretion of the investigator. If not conducted, the child must have been able to fix and follow. Females were not pregnant or lactating and must have been surgically sterilized or utilizing suitable contraception if they were not premenarcheal or postmenopausal. All females who were of childbearing potential (i.e., who were premenopausal or had not been surgically sterilized) were required to have a negative pregnancy test prior to receiving drug at Day 1 and must not have intended to become pregnant during the study.

Exclusion Criteria

- Presence of signs and symptoms of bacterial conjunctivitis for longer than 7 days prior to entry into the study.
- Presence of concomitant viral infection of the urinary or gastrointestinal tract.
- Presence of inflammation and/or active structural change in the cornea, iris or anterior chamber at the Day 1 (Screening/Baseline) visit.
- Presence of corneal opacity or any corneal abnormality that would impact the outcome of the study at the Day 1 (Screening/Baseline) visit.
- Presence of nasolacrimal duct obstruction.
- Infants less than one year of age with suspected or confirmed ophthalmia neonatorum of gonococcal, chlamydia, herpetic, or chemical origin.
- Infants less than one year of age whose birth mothers had any sexually transmitted disease within one month prior to delivery.
- Infants less than one year of age with family histories of congenital cataracts, retinoblastoma, or other relevant genetic disorders, or those undergoing treatment for retinopathy of prematurity (i.e., progressed beyond the observation threshold and actively being treated).
- Contact lens wear during the course of the study.
- Only one sighted eye or vision in either eye not correctable to 0.6 or better logMAR in both eyes using ETDRS chart or an age-appropriate measurement method supplied by the Sponsor. Visual acuity measurement for children less than 3 years of age was conducted at the discretion of the investigator. If not conducted, child was able to fix and follow. Visual acuity was to be measured using the same method for each patient at each visit.
- Abnormal findings in the posterior pole of the retina or any media opacity found in a fundus examination at the Day 1 (screening/Baseline) visit.
- Suspected fungal, viral (e.g., Herpes simplex) or Acanthamoeba infection, based on clinical observation.
- Use of any preserved topical ocular medication at the time of entry into the study or during study participation. Non-preserved tear substitutes were allowed.
- Use of any oral or topical ocular antibacterial agent within the 72 hours prior to study entry or during study participation.
- Use of systemic steroids within 14 days prior to study entry. Use of topical ocular steroids or nonsteroidal anti-inflammatories (NSAIDs) within one week prior to study entry. Use of these medications is not allowed during study participation. Use of nasal inhaled steroids is not allowed during the study. Bronchial steroids by inhaler were

allowed, however, nebulized steroids were excluded. Topical dermal steroids were allowed.

- Use of systemic nonsteroidal anti-inflammatories (NSAIDs) within 24 hours prior to study entry or at any time during the study unless the patient has been on a steady (not as needed) treatment regimen for at least 2 months prior to entry and the therapy will continue throughout the study. Acetaminophen (e.g. Tylenol) PRN was allowed.
- Any systemic or ocular disease or disorder, complicating factors, or structural abnormality that would negatively affect the conduct or outcome of the study (e.g., hepatitis, acute or chronic renal insufficiency).
- Any current immunosuppressive disorder (e.g., HIV-positive), or use of immunosuppressive therapy (including chemotherapy).
- Known or suspected allergy or hypersensitivity to fluoroquinolones.
- Pregnant or lactating women, women who had a positive urine pregnancy test, or women of childbearing potential who were not using adequate birth control to prevent pregnancy.
- Participation in any other investigational clinical study within 30 days prior to study enrollment.
- Any patient who had a family member currently enrolled in this study.
- Any patient previously enrolled in this study.
- Any patient who was on staff at the investigational site or is a family member of staff personnel.
- Additionally, the Medical Monitor declared any patient ineligible for a sound medical reason.

Primary Efficacy

The primary clinical efficacy variable was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection (bulbar conjunctival injection and conjunctival discharge/exudate). Clinical cure was attained when the sum of the two cardinal ocular signs was zero (i.e., normal or absent) at Day 7. The primary microbiological efficacy variable was the bacterial eradication rate at the Exit visit.

Secondary Efficacy

The secondary efficacy variables were the eight individual signs and symptoms of bacterial conjunctivitis at each visit (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia).

Analysis

The primary statistical objective of the study was to demonstrate that Moxifloxacin AF Ophthalmic Solution was superior to Moxifloxacin AF Vehicle in the treatment of bacterial conjunctivitis. Primary efficacy had two components, clinical and microbiological.

Investigators

Investigator	Investigator #	# enrolled
Cavanagh, Dwight H. M.D. Dallas, TX	1678	6
Christensen Shane G., M.D. Salt Lake City, UT	2833	29
Coopersmith, Kathie, M.D. Ogden, UT	4120	No Patients Enrolled
Davitt, William F., M.D. El Paso, TX	3802	5
DeLeon, Liberation, M.D. Paramount, CA	3545	36
Denyer, Garth C., M.D. Spring, TX	4796	27
Duke, Anton L., M.D. Little Rock, AR	4054	15
Henry, Dan C., M.D. Salt Lake City, UT	1689	24
Hughes, Jane, M.D. San Antonio, TX	3664	No Patients Enrolled
Hirschfield, Jeffrey, A., M.D. St. Petersburg, FL	3568	No Patients Enrolled
Ituaga, Angeline, Y., M.D. Anaheim, CA	4580	36
Jones, Ronald C., M.D. Provo, UT	3475	3
Kanengiser, Bruce, M.D. Piscataway, NJ	3458	7
Kerlin, Joseph, M.D. Avon, IN	3385	28
Khan, Farha, M.D. Phoenix, AZ	4744	24
Lauret, Michael H., M.D. Provo, UT	3455	2
Levin, Michael L., M.D. Las Vegas, NV	3535	22
Macy, Jonathan I., M.D. Los Angeles, CA	2029	No Patients Enrolled
Maira, Rosa, D.O. Portage, MI	4053	23
Moscovic, Dean, M.D. Clarkston, MI	5007	11
Parker, Wiliam D., M.D. Shreveport, LA	2475	26
Peltier, Chrs B., M.D.	4056	5

Cincinnati, OH		
Perez-Ortiz, Don, M.D. Tampa, FL	4042	15
Plunkett, Stephanie, M.D. Salt Lake City, UT	5008	1
Raikel, Marina, M.D. Torrance, CA	3401	24
Reyes, Elizabeth, M.D. Anaheim, CA	5007	No Patients Enrolled
Scheidell, Renee, M.D. West Jordan, UT	4061	36
Scoper, Stephen V., M.D. Virginia	1238	No Patients Enrolled
Seitzman, Gerami, M.D. Baltimore, MD	4368	21
Silas, Peter E., M.D. Layton, UT	3463	35
Simon, Michael W., M.D. Lexington, KY	4576	22
Skaug, Warren, A., M.D. Jonesboro, AR	4055	36
Sokolov, Ronald M.D. Sacramento, CA	3130	35
Steingard, Joseph J., M.D. Philadelphia, PA	4140	1
Sultana, Nighat, M.D. The Woodlands, TX	4795	36
Tandon, Smita, M.D. Fountain Valley, CA	3633	36
Tepedino, Michael M.D. High Point, NC	3626	11
Watson, Randall L., M.D. West Jordan, UT	3319	23

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

Study #2 C-04-40

Title: An Evaluation of the Safety and Efficacy of Moxifloxacin AF Ophthalmic Solution 0.5% for the Treatment of Bacterial Conjunctivitis in India.

Study Design

This was a prospective, multi-center, double-masked, parallel-group, randomized study, designed to evaluate the efficacy and safety of Moxifloxacin AF Ophthalmic Solution compared to VIGAMOX Ophthalmic Solution 0.5% in the treatment of bacterial conjunctivitis. Patients

Clinical Review

{Jennifer D. Harris, MD}

{NDA 22-428}

(b) (4) (moxifloxacin AF)

enrolled were at least one month of age or older, of any race and either sex. Eligible patients who met all the inclusion and exclusion criteria were randomized into one of two treatment groups; Moxifloxacin AF Ophthalmic Solution, one drop two times a day (morning and bedtime) and one drop of vehicle once a day (midday); or VIGAMOX one drop, three times a day (morning, midday, and bedtime).

Approximately 675 patients with a clinical diagnosis of bacterial conjunctivitis were targeted for enrollment to achieve at least 370 (185 on Moxifloxacin AF and 185 on VIGAMOX) bacterial pathogen positive patients. If the pathogen positive rate was lower than the expected rate of 55%, the protocol allowed for additional patients to be enrolled to reach the target of 370 pathogen positive patients.

Protocol C-04-40 Study Plan

Parameters	Day 1 Screening/ Baseline	Day 3 (-1)	Day 4 (EOT) 12-48 hours post- last dose	Exit Visit (TOC)^a 60-97 Hrs post-last dose
Screen for inclusion/exclusion criteria	X			
Informed Consent	X			
Urine Pregnancy Test ^b	X			X
General Information: Medical History	X			
Changes in concomitant medication or general health	X	X	X	X
Patients Rate Ocular symptoms		X	X	X
Visual Acuity	X	X	X	X
Investigator Rates Ocular Signs	X	X	X	X
Evaluation of Cornea and Iris/Anterior Chamber	X	X	X	X
Collect Ocular Microbiological specimens ^c	X			X
Dilated Fundus Exam of posterior pole	X		X	X
First Dose of Study Medication (in clinic)	X			
Dispense Study Medication ^d	X	X		
Record Adverse Events	X ^e	X	X	X
Collect Study Medication ^d		X	X	X
Complete Exit Form ^a				X

^a At any time a patient exits from the study.

^b For women of child-bearing potential, before instillation of study medication and at exit from the study.

^c At Day 1 and at any time a patient exits from the study. The specimens must be collected prior to the fundus exam.

^d As needed.

^e After dosing.

Inclusion Criteria

1. Be one month of age or older, of any race and either sex.
2. Have a diagnosis of bacterial conjunctivitis based on clinical observation.
 - a. All patients must have a rating ≥ 1 for bulbar conjunctival injection and a rating ≥ 1 for conjunctival discharge / exudate in at least one eye (the same eye) at the Day 1 visit, and
 - b. All patients must experience some matting in the affected eye(s).
3. Must be able to understand and sign an informed consent form that has been approved by an Independent Ethics committee (IEC). If the patient is under 18 years of age, the

informed consent (IC) must be understood and signed by the patient's legally authorized representative (parent or guardian).

4. Must agree to comply with the visit schedule and other requirements of the study. The parent or guardian must agree to ensure compliance of patients less than 18 years of age.
5. Females who are not pregnant and are not lactating. All females of childbearing potential (those who are not pre-menarcheal, not postmenopausal or surgically sterile) may participate only if they have a negative urine pregnancy test prior to randomization, and if they agree to use adequate birth control methods to prevent pregnancy throughout the study. Adequate birth control methods include hormonal- topical, oral, implanted or injected contraceptives; mechanical- spermicide in conjunction with a barrier such as a condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner.

Exclusion Criteria

Same as Study C-04-38

Efficacy

The primary clinical efficacy variable was clinical cure. Clinical cure was achieved when the sum of the ratings for the cardinal ocular signs (bulbar conjunctival injection and conjunctival discharge/exudate) was zero (i.e. normal or absent) at the Toc visit (Day 7).

The primary microbiological efficacy variable was microbiological success. Microbiological success was achieved when the pre-therapy pathogens were eradicated at TOC.

Secondary efficacy variables were measured in this study. These were the eight individual signs and symptoms of bacterial conjunctivitis at each visit (bulbar conjunctival injection, conjunctival discharge/exudate, lid erythema, lid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia).

Analysis

The primary statistical objective of this study was to demonstrate the non-inferiority of Moxifloxacin AF Ophthalmic Solution relative to VIGAMOX in the treatment of bacterial conjunctivitis. Primary efficacy had two components, clinical and microbiological.

Investigators

Investigator	Investigator #	# enrolled
Dr. Naheed Abidi	4731	15
Dr. Gurkirat S. Bajwa	4615	48
Dr. Ganesh Balasubramaniam	3070	48

Dr. Samar Basak	4606	48
Dr. Yasmin R. Bhagat	3051	48
Dr. P.N. Biswas	4603	32
Dr. Andrew David Braganza	4610	8
Dr. Anupam A. Deshpande	4803	26
Dr. Prashant Garg	3071	10
Dr. Ina Jain	4736	30
Dr. Nelson Jesudasan, C.A.	3053	48
Dr. Shreekant B. Kelkar	3054	38
Dr. Dipak Kumar	4614	8
Dr. P.K. Mathur	4617	4
Dr. Rahin H. Muljiani	4621	32
Dr. Srinivasan Muthiah	4613	43
Dr. Pravada Narayanan	4619	22
Dr. Rama Rajagopal	4609	7
Dr. Revathi Rajaraman	4612	16
Dr. Manjoo S.Reddy	4602	20
Dr. Rahul A. Shroff	4605	10
Dr. Hemkala Trivedi	4618	32
Dr. Pushpa Varma	4604	32
Dr. S. Viswanathan	4611	38
Dr. Usha H. Vyas	3059	32

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Treatment of bacterial conjunctivitis in patients ≥ 1 year of age.

6.1.1 Methods

Description of the clinical trial design is contained in section 5.3.

6.1.2 Demographics

Patient Demographics

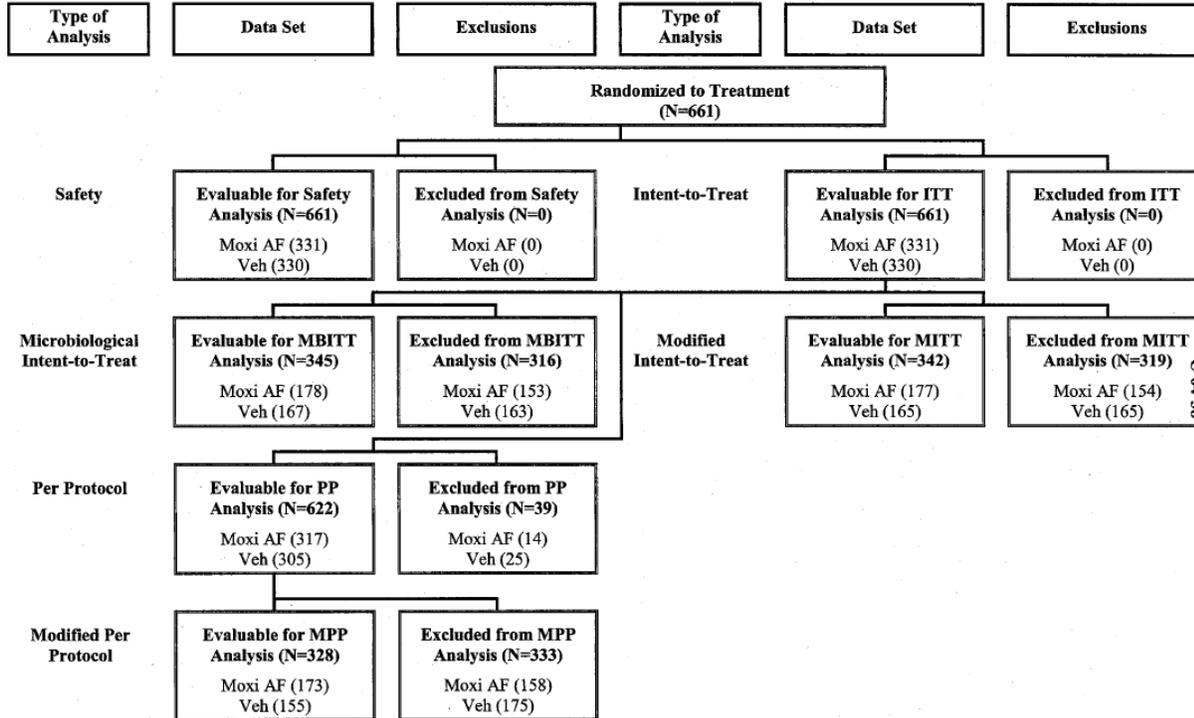
		Study	
		C-04-38	C-04-40
Total enrollment in study		661	695
Race	White	560	
	Black or African American	49	
	Asian	10	695
	Native Hawaiian	1	
	American Indian	1	
	Other	37	
	Multi-Racial	3	
Age	28 days to 23 months	113	12
	2 to 11 years	241	52
	12 to 17 years	66	32
	18 to 64 years	226	537
	≥ 65 years	15	62
Sex	Male	288	461
	Female	373	234
Iris color	Brown	353	693
	Blue	190	
	Hazel	82	
	Green	31	
	Grey	5	2
Culture positive	Yes	345	382
	No	316	313

Distribution of Culture Positive Patients, 1 month to 6 Years of Age, Exposed to Moxifloxacin AF Ophthalmic Solution

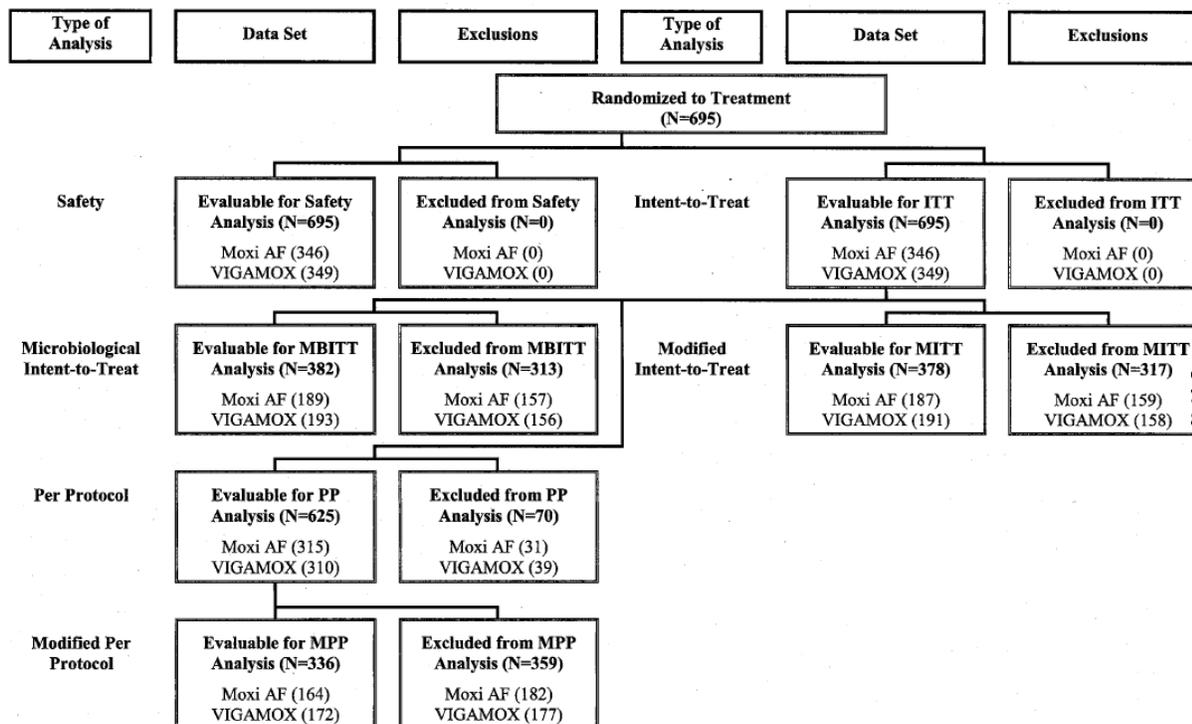
Age	Study	
	C-04-38	C-04-40
Less than 6 months	3/16	2/2
6 months to < 1 year	6/16	0/1
1 year	8/30	1/3
2 years	5/19	1/2
3 years	4/26	2/3
4 years	4/14	0/2
5 years	3/11	0/0
6 years	9/15	0/1

6.1.3 Subject Disposition

Study C-04-38 Subject Disposition



Study C-04-40 Subject Disposition



6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for study C-04-38 and C-04-40 was the clinical cure rate of the two ocular signs of bacterial conjunctival infection (bulbar conjunctival injection and conjunctival discharge/exudate) at the Exit visit (day 7). Clinical cure was attained when the sum of the two ocular signs was zero. The primary microbiological endpoint was the bacterial eradication rate at the Exit visit (day 7).

The statistical objective for study C-04-38 was to demonstrate that moxifloxacin AF was superior to vehicle in the in the MITT population.

The statistical objective for study C-04-40 was to demonstrate the non-inferiority of moxifloxacin AF to Vigamox in the MPP population.

Analysis Populations:

Safety: All patients who received drug.

Intent-to-Treat (ITT): All patients who received drug and had at least one on-therapy visit.
Microbiological Intent-to-Treat (MBITT): All patients who received drug, had at least one on-therapy visit and were pathogen positive for bacteria on Day 1.

Modified Intent-to-Treat (MITT): All patients who received drug, had at least one on therapy visit, met pre-randomization inclusion and exclusion criteria and were pathogen positive for bacteria on Day 1.

Per Protocol (PP): All patients who received drug, met pre-randomization inclusion and exclusion criteria and had baseline and test of cure (or exit if the patient exited from the study early) visits.

Modified Per Protocol (MPP): All patients who received drug, met pre-randomization inclusion and exclusion criteria, had baseline and test of cure (or exit if the patient exited from the study early) visits and were pathogen positive for bacteria on Day 1.

The planned primary efficacy endpoints for this study were clinical cure (bulbar conjunctival injection+0, normal and conjunctival discharge/exudate=0, absent) and microbiological success (bacterial eradication of pre-therapy pathogens) at the Day 7 [exit/test-of-cure (TOC)] visit.

Study C-04-38

	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	129 (72.5%)	128 (72.3%)	105 (75%)
Vehicle	113 (67.7%)	111 (67.3%)	88 (66.2%)
p-value	0.3295	0.3097	0.1089

	Microbiological Success at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	150 (84.3%)	149 (84.2%)	115 (82.7%)
Vehicle	110 (65.9%)	109 (66.1%)	90 (67.7%)
p-value	< 0.0001	0.0001	0.0039

Comment: The Agency informed the sponsor during development that the MBITT population would be used for the efficacy evaluation. The study failed to demonstrate efficacy for clinical cure at day 7. The MITT and MPP population results are consistent with the MBITT population.

Study C-04-40

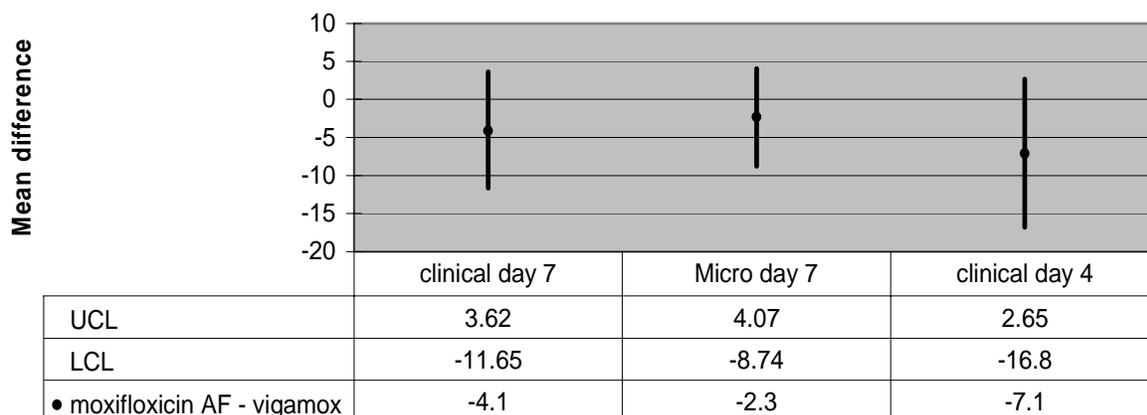
	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	152 (80.4%)	150 (80.2%)	103 (84.4%)
Vigamox	163 (84.5%)	161 (84.3%)	108 (85.7%)
p-value	0.30	0.3	0.78
Delta	-4.1	-4.1	-1.3
LCL	-11.65	-11.78	-10.16
UCL	3.62	3.62	7.59

	Microbiological Success at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	165 (87.3%)	163 (87.2%)	112 (92.6%)
Vigamox	173 (89.6%)	171 (89.5%)	115 (92%)
p-value	0.48	0.47	0.87
Delta	-2.3	-2.3	0.6
LCL	-8.74	-8.8	-6.11
UCL	4.07	4.1	7.23

(b) (4)
 Initial review of the available efficacy data suggests that an acceptable non-inferiority margin for topical anti-infectives may be in the range of 2%-6%. The results of this trial suggest that Moxifloxacin AF is inferior to Vigamox for both clinical cure and microbiological success.

Additionally, the dosing regimen used in this trial for Vigamox is inconsistent with the regimen use in the approval for this product. The clinical trials conducted to establish the efficacy of Vigamox were conducted with the drug dosed for 4 days. Clinical cure rates at the end-of-therapy visit (day5) ranged from 66-69% and 83-87% at test of cure (day 7). In the current study (C-04-40) Vigamox is dosed for only 3 days in the comparator arm. This is not the optimum dosing frequency and is not the regimen used in the clinical trials to establish efficacy. The clinical cure rate is 58% at the end-of-therapy (day 4) and approximately 84-85% at the test-of-cure visit (day 7). The difference in dosing regimen and evaluation timepoints makes the use of any non-inferiority margin problematic for this trial.

Primary Efficacy (non-Inferiority study) MBITT population - Study C-04-40



6.1.5 Analysis of Secondary Endpoints(s)

The planned secondary endpoints for this study included the eight individual signs and symptoms of bacterial conjunctivitis at each visit (i.e., bulbar conjunctival injection, conjunctival discharge/exudate, lid erythema, lid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia).

A full analysis of the secondary endpoints will be conducted for potential inclusion in the label once efficacy has been demonstrated for this product.

6.1.6 Other Endpoints

Exploratory analyses included an evaluation of early clinical cure at Day 4 (EOT) visit. A cure for this analysis was defined as a patient who was cured at Day 4 and remained cured at the exit/TOC visit.

Study C-04-38

	Clinical Cure at Day 4		
	MBITT	MITT	MPP
Moxifloxacin AF	104 (58.4%)	103 (58.2%)	80 (60.6%)
Vehicle	78 (46.7%)	77 (46.7%)	54 (44.3%)
p-value	0.0293	0.0329	0.0091

Note: Microbiological specimens were only collected on Day 1 and Day 7 (exit/TOC).

A clinical cure rate by investigator was performed by the sponsor for the MITT and MPP populations. A review of this analysis shows that for the MITT population, only 2 investigators had a statistically significant results in clinical cure rate: #4055 and #4795. These investigators were two of the highest enrollers with 36 patients each. Investigator #4055 and #4795 had pathogen positive patients of 15 and 20 respectively.

Study C-04-40

	Clinical Cure at Day 4		
	MBITT	MITT	MPP
Moxifloxacin AF	109 (57.7%)	108 (57.8%)	73 (62.4%)
Vigamox	125 (64.8%)	123 (64.4%)	80 (65%)
p-value	0.16	0.19	0.67
Delta	-7.1	-6.6	-2.6
LCL	-16.8	-16.45	-14.82
UCL	2.65	3.17	9.52

Note: Microbiological specimens were only collected on Day 1 and Day 7 (exit/TOC).

The efficacy results on day 4 are consistent with the primary efficacy endpoint on day 7. Moxifloxacin AF is inferior to Moxifloxacin.

6.1.7 Subpopulations

The primary efficacy endpoint (clinical cure and microbiological success) as well as early clinical cure at Day 4 were analyzed in study C-04-38 for each of the investigators and for the following subgroups: age (28 days to 23 months, 2-11 years, 12-17 years, 18-64 years and age ≥ 65, sex, race, ethnicity, iris color, affected eye(s) and study eye.

In general, the results of the subgroup analysis for Study C-04-38 follow the same trend as the overall efficacy analysis. However, the endpoint of microbiological success at Day 7 appears to be driven by the 2-11 age group subset. This is likely due to this age group comprising 40% of all pathogen positive subjects in the trial.

MBITT – Microbiological Success at Exit (TOC) Study C-04-38

Age	Treatment	Total		Success		p-value
		N	N	%		
28 days – 23 months	Moxifloxacin AF	45	29	64.4%	0.95	
	Vehicle	43	28	65.1		
2-11 years	Moxifloxacin AF	71	62	87.3	0.0014	
	Vehicle	70	45	64.3		
12-17 years	Moxifloxacin AF	11	10	90.9	0.57	
	Vehicle	9	7	77.8		
18-64 years	Moxifloxacin AF	46	44	95.7	0.0023	
	Vehicle	39	28	71.8		
≥ 65 years	Moxifloxacin Af	5	5	100	0.06	
	Vehicle	6	2	33.3		

The positive results for the exploratory analysis of early clinical cure at Day 4 appears to be driven by the 28 day- 23 month old age group.

MBITT – Early Clinical Cure at Day 4 (EOT) Study C-04-38

Age	Treatment	Total		Success		p-value
		N	N	%		
28 days – 23 months	Moxifloxacin AF	45	35	77.8	0.0025	
	Vehicle	43	20	46.5		
2-11 years	Moxifloxacin AF	71	45	63.4	0.1512	
	Vehicle	70	36	51.4		
12-17 years	Moxifloxacin AF	11	6	54.5	0.41	
	Vehicle	9	3	33.3		
18-64 years	Moxifloxacin AF	46	32	69.6	0.21	
	Vehicle	39	22	56.4		
≥ 65 years	Moxifloxacin AF	5	4	80	0.08	
	Vehicle	6	1	16.7		

The subgroup analyses for study C-04-40 for age, sex, affected eye and study eye are consistent with the overall study results.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The concentration of 0.5% moxifloxacin was chosen for Moxifloxacin AF based on the efficacy and safety of Vigamox. The modified formulation contains a xanthan gum (b) (4)

Clinical Review

{Jennifer D. Harris, MD}

{NDA 22-428}

(b) (4) (moxifloxacin AF)

surface with the objective of maintaining similar efficacy to Vigamox with reduced dosing (i.e. two times a day versus three times a day).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

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

6.1.10 Additional Efficacy Issues/Analyses

Organism Eradication rates at day 6 for organisms present in ≥ 5 infections in patients treated with moxifloxacin AF - Study C-04-38

Organism	Moxifloxacin AF		vehicle		Moxifloxacin AF		Vigamox		*Total infections/ eradication rate
	# of infections	# eradicated							
Streptococcus pneumoniae	28	25	8	7	-	-	-	-	28/89%
Propionibacterium acnes	25	24	26	22	-	-	-	-	25/96%
Staphylococcus epidermidis	20	20	21	19	33	33	33	33	53/100%
Staphylococcus aureus	7	7	7	5	12	12	10	10	19/100%
Staphylococcus capitis	3	3	-	-	3	3	-	-	6/100%
Staphylococcus arlettae	-	-	-	-	8	8	7	7	8/100%
Staphylococcus haemolyticus	-	-	-	-	6	6	14	12	6/100%

Staphylococcus hominis	2	2	-	-	4	4	-	-	6/100%
Haemophilus influenzae	45	32	42	-	-	-	-	-	45/71%

Microorganisms listed in this table are those that potentially will be recommended for inclusion in the indications section of any future labeling for this product. Recommendations are based on the following criteria:

- *Organism has been cultured from an eye with conjunctivitis and treated with moxifloxacin AF in 10 or more cases with a $\geq 50\%$ eradication rate.*
- *Organism has been cultured from an eye with conjunctivitis and treated with moxifloxacin AF in 5-9 cases with a $\geq 80\%$ eradication rate.*
- *Organisms that are cultured in less than 5 infections are not listed and will not be included in the label.*

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
C-05-15 Multiple dose topical ocular PK/safety study	Multiple-dose, double-masked, randomized, vehicle – controlled, parallel-group	Healthy adult male and female volunteers	Moxifloxacin AF ophthalmic solution Vehicle	1 drop BID OU 1 drop BID OU	4 days with final dose on morning of Day 5	30
C-04-38 Safety/efficacy study	Prospective, randomized, vehicle-controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution Vehicle	1 drop BID OU 1 drop BID OU	3 days	661 (345 culture positive diagnosed eye)
C-04-40 Safety/efficacy study	Prospective, randomized, active-controlled, double-masked	Patients 1 month of age and older with bacterial conjunctivitis	Moxifloxacin AF ophthalmic solution <u>and</u> Vehicle Vigamox	1 drop BID OU <u>and</u> 1 drop BID OU 1 drop TID OU	3 days	695 (382 culture positive diagnosed eye)

7.1.2 Categorization of Adverse Events

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

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

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

Adverse events were evaluated individually for each study. Due to the size of the data base, the pooled data was not used in the review.

7.2 Adequacy of Safety Assessments

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

A total of 697 patients were exposed to moxifloxacin AF during development.

Overview of Exposure to Study Drug by Protocol

Protocol Number	Safety N	Moxifloxacin AF	Vigamox	Vehicle
C-04-38	661	331		330
C-04-40	695	346	349	
C-05-15	30	20		10

The age distribution of the patients exposed to moxifloxacin during development is as follows:

Age group	Number exposed
28 days to 23 months	68
2 to 11 years	143
12 to 17 years	38
18 to 64 years	399
65 years or older	39

The majority (85-97%) of patients in each age group were exposed to moxifloxacin AF for 3 days with another 2-8% exposed to a total of 4 days of drug.

7.2.2 Explorations for Dose Response

Moxifloxacin AF was administered in one dose level (1 drop twice a day for three days) for each of the phase 3 studies. No dose response information was obtained.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with Moxifloxacin AF.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

Based on in vitro studies conducted on moxifloxacin and contained in the original NDA, moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 and therefore is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

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

The adverse events reported during the development of moxifloxacin AF are consistent with other topical quinolones. The assessment of these adverse events within the clinical trials were adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the clinical development of moxifloxacin AF.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported during the clinical development of moxifloxacin AF.

7.3.3 Dropouts and/or Discontinuations

Reason for discontinuation	C-04-38		C-04-40	
	Moxifloxacin AF	Vehicle	Moxifloxacin AF	Vigamox
Adverse Event	5	5	3	1
Lost to follow-Up	3	6	24	25
Decision	5	5	2	2

Unrelated to an Adverse Event				
Noncompliance	1	8	0	1
Treatment Failure	7	32	7	13
Other	1	4	0	0

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

Adverse Events Associated with Discontinuation – Study C-04-38

Patient	Age	Sex	Treatment	Onset day	Adverse event
1720	48	F	Moxifloxacin AF	1	Foreign body sensation, increased lacrimation, conjunctival disorder
2005	32	M	Moxifloxacin AF	2	gonorrhea
1314	19	F	Moxifloxacin AF	2	Streptococcal pharyngitis
2218	1	M	Moxifloxacin AF	5	Sinusitis
102	15	M	Moxifloxacin AF	3	Conjunctivitis
405	1	M	Vehicle	2	Otitis Media
1312	3	M	Vehicle	4	Otitis media
2126	2	M	Vehicle	1	Periorbital cellulitis
926	42	F	Vehicle	5	conjunctivitis
104	41	M	Vehicle	4	Uveitis

Adverse Events Associated with Discontinuation – Study C-04-40

Patient	Age	Sex	Treatment	Onset day	Adverse event
3413	21	M	Moxifloxacin AF	2	Conjunctival edema, eyelid edema, ocular hyperemia
2422	41	M	Moxifloxacin AF	6	Conjunctival ulcer
4007	9	M	Moxifloxacin AF	1	Rhinitis, corneal opacity, punctuate keratitis, nasal congestion, pyrexia
3408	24	M	Vigamox	3	Conjunctival edema, eye pruritus, eyelid edema

7.3.4 Significant Adverse Events

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

7.3.5 Submission Specific Primary Safety Concerns

N/A – no specific safety issues identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Adverse Events (rate ≥ 1%) – Safety Population – study C-04-38

Adverse Event	Moxifloxacin AF N=331		Vehicle N=330	
	N	%	N	%
<i>Eye disorders</i>				
Conjunctivitis	5	1.5	5	1.5
<i>Infections and infestations</i>				
Upper respiratory tract infection	6	1.8	5	1.5
Otitis media	2	0.6	6	1.8
<i>Nervous system disorders</i>				
Headache	0	0	6	1.8
<i>General disorders and administration site conditions</i>				
Pyrexia	2	0.6	4	1.2

Common Adverse Events (rate ≥ 1%) – Safety Population – study C-04-40

Adverse Event	Moxifloxacin AF N=346		Vigamox N=349	
	N	%	N	%
<i>Eye disorders</i>				
Eye irritation	8	2.3	5	1.4
Eye pain	8	2.3	7	2.0
Conjunctivitis	5	1.4	2	0.6
Punctuate keratitis	5	1.4	5	1.4
Eye pruritus	1	0.3	5	1.4
<i>General disorders and administration site conditions</i>				
Pyrexia	7	2.0	7	2.0

7.4.2 Laboratory Findings

Clinical laboratory evaluations were analyzed in one pharmacokinetic study (C-05-15) which involved 30 healthy male and female patients (19 to 73 years of age). Laboratory test including hematology, blood chemistry and urinalysis results were evaluated in all patients at baseline and exit.

There were statistically significant changes from baseline for both moxifloxacin AF and the vehicle in several hematology and blood chemistry parameters. However, these changes were not clinically relevant and each remained within the normal range.

There were no statistically significant changes in urinalysis measurements for either moxifloxacin AF or the vehicle.

7.4.3 Vital Signs

Cardiovascular parameters (pulse and blood pressure) were measured at screening, day 1 and the exit visit. Any clinically relevant changes from baseline were reported as an adverse event. No adverse events were reported for the cardiovascular parameters during the study. No clinically relevant changes in cardiovascular parameters were observed. No clinically relevant differences between the treatment groups were identified.

7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECGs were obtained at baseline and the exit visit. There were no clinically relevant changes reported within groups or between groups for moxifloxacin and the vehicle group.

7.4.5 Special Safety Studies/Clinical Trials

N/A – There were no special safety studies conducted for this product.

7.4.6 Immunogenicity

N/A – immunogenicity testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Moxifloxacin AF was administered in one dose level (1 drop twice a day for three days) for each of the phase 3 studies. No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

N/A – Moxifloxacin does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

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

7.5.4 Drug-Disease Interactions

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

7.5.5 Drug-Drug Interactions

No drug interactions were reported in any clinical study involving Moxifloxacin AF.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted. In addition, long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. An accelerated study with initiators and promoters was conducted in rats and moxifloxacin was not found to be carcinogenic. (see original review/label for Vigamox).

7.6.2 Human Reproduction and Pregnancy Data

The clinical study protocols involving moxifloxacin AF excluded the participation of pregnant or breast-feeding females. No information was obtained on its use in these populations.

7.6.3 Pediatrics and Assessment of Effects on Growth

Based on the review of the original NDA for Vigamox, there is no evidence that the ophthalmic administration of moxifloxacin has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No information is available on overdosage in humans. No reports of overdose were received during the clinical studies of moxifloxacin AF. In an oral (gavage) monkey study of moxifloxacin, doses up to 15mg/kg/day did not produce any toxicity. This dose is at least ten times higher than the accidental dose of one bottle of moxifloxacin AF, 5 mg/mL for a 10 kg child.

There was no evidence of drug abuse reported in the clinical trials. And there were no reports of withdrawal or rebound phenomena.

7.7 Additional Submissions

The 120 day safety update contains results from two new clinical trials.

C-07-12 is a one day pharmacokinetic study in patients undergoing cataract surgery. Sixty-five (65) patients were assigned to the moxifloxacin AF group and 65 were assigned to the Vigamox group. There were no deaths or serious adverse events reported.

C-07-40 is a clinical trial in patients with bacterial conjunctivitis. This trial is ongoing and no deaths or serious adverse events have been reported. One additional patient has discontinued the study due to ulcerative colitis.

A review of the additional data contained in the 120-day safety update does not change the conclusions about the overall safety profile of moxifloxacin AF contained in the original NDA submission.

8 Postmarket Experience

Moxifloxacin AF is not marketed in any country. Moxifloxacin hydrochloride ophthalmic solution, 0.5% base is approved in more than 50 countries. It was approved in the U.S. in 2003. The sponsor has received 471 spontaneous adverse event reports worldwide associated with moxifloxacin. Thirty-five (35) were considered serious. The spontaneous postmarketing reports for moxifloxacin is consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with moxifloxacin.

9 Appendices

9.1 Literature Review/References

N/A – an independent literature review was not conducted for this application.

9.2 Labeling Recommendations

N/A - Labeling is not recommended for this product at this time.

9.3 Advisory Committee Meeting

N/A – an advisory committee meeting is not required for this application.

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

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

/s/

JENNIFER D HARRIS
08/12/2009

WILLIAM M BOYD
08/12/2009

WILEY A CHAMBERS
08/12/2009