OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-428
Submission Date(s):	20MAY2010
Brand Name	TBD
Generic Name	Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5%
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
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Applicant	Alcon Research, Ltd.
Relevant IND(s)	IND 59,944
Submission Type; Code	Class 2 Resubmission
Formulation; Strength(s)	Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5%
Indication	Treatment of bacterial conjunctivitis

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1. EXECUTIVE SUMMARY

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 dosing regimen of VIGAMOX is one drop in the affected eye three times a day for seven days. The currently proposed product Moxifloxacin AF contains a retention-enhancing vehicle expected to provide similar efficacy and safety to VIGAMOX® with a reduced dosing frequency. 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 original NDA submission for Moxifloxacin AF Ophthalmic Solution dated December 15, 2008 contained 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). These studies were reviewed by the Office of Clinical Pharmacology (review of the original NDA submission dated July 15, 2009). A Complete Response letter was issued on October 7, 2009 citing a lack of substantial evidence demonstrating that Moxifloxacin AF when dosed two times per day for three days was superior to vehicle in the treatment of bacterial conjunctivitis in patients one month of age and older. To address this issue, at least one additional adequate and well-controlled clinical study demonstrating the efficacy of moxifloxacin hydrochloride ophthalmic solution 0.5% as base for the treatment of bacterial conjunctivitis was required.

The current submission (NDA 22-428 Class 2 Resubmission dated May 20. 2010) contains two clinical studies: an additional vehicle-controlled, multiple-dose, pivotal trial designed to address the issues outlined in the Complete Response (Study C-07-40) and a clinical pharmacology study investigating moxifloxacin concentrations in conjunctival tissue and aqueous humor following administration of single doses of Moxifloxacin AF and VIGAMOX in cataract patients (Study C-07-12). The clinical pharmacology information provided by the Applicant in this resubmission is acceptable. The pharmacokinetic data previously submitted with the original NDA 22-428 addresses the requirement for an assessment of in vivo bioavailability outlined in 21 CFR 320.21. Data from Study C-07-12 should be used for informational purposes only.

1.1. Recommendation

The clinical pharmacology information provided by the Applicant is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

Moxifloxacin AF 0.5%, a sterile solution for topical ophthalmic use, is proposed for the treatment of bacterial conjunctivitis. In addition to a vehicle-controlled, multiple-dose, pivotal trial (Study C-07-40) designed to address the issues outlined in the Complete Response issued October 7, 2009, the current submission (NDA 22-428 Class 2 Resubmission) contains one clinical pharmacology study investigating moxifloxacin concentrations in conjunctival tissue and aqueous humor following administration of single doses of Moxifloxacin AF and VIGAMOX in cataract patients (Study C-07-12). The clinical pharmacology findings from this study are as follows:

- Data from Study C-07-12 suggests concentrations of moxifloxacin in conjunctiva and aqueous humor following a single dose of Moxifloxacin AF in cataract patients were significantly greater relative to those from patients treated with VIGAMOX.
- The clinical relevance of these differences in concentrations between the two moxifloxacin ophthalmic formulations has not been established.
- The adequacy of the assay methodology for determination of moxifloxacin concentrations in conjunctival tissues from cataract patients could not be determined.

The pharmacokinetic data previously submitted with the original NDA 22-428 addresses requirement for bioavailability outlined in 21 CFR 320.21. Data from Study C-07-12 should be used for informational purposes only, since 1) questions remain regarding the adequacy of the assay used to measure conjunctival concentrations, and 2) conjunctival and aqueous humor concentrations have not been shown to be relevant to the clinical indication.

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Team Leader

cc:
Division File: NDA 22-428
HFD-520 (CSO/Gorski)
HFD-520 (MO/Lim)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)

2. QUESTION BASED REVIEW

Since this submission is an NDA for a locally administered ophthalmic drug product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

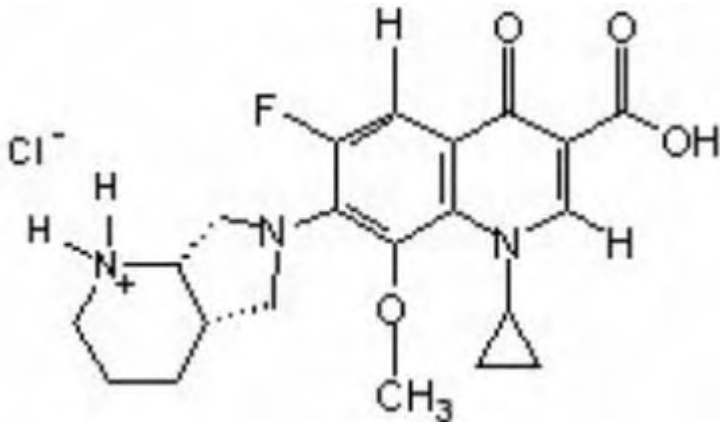
2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Moxifloxacin AF ophthalmic solution, 0.5% is a sterile, stable, self-preserved ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride, equivalent to 0.5% moxifloxacin. Moxifloxacin AF is a greenish-yellow, isotonic solution with an osmolality of 300-370 mOsm/kg and a pH of approximately 7.4. Moxifloxacin hydrochloride is a slightly yellow to yellow crystalline powder. Each mL of Moxifloxacin AF contains 5.45 mg moxifloxacin hydrochloride, equivalent to 5 mg moxifloxacin base.

Structural Formula: $C_{21}H_{24}FN_3O_4 \cdot HCl$

Chemical Structure:



Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolol[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

Compendial Name: Moxifloxacin Hydrochloride (USAN)

International Nonproprietary Name (INN): Moxifloxacin

Company Laboratory Code: AL-15469A, BAY 12-8039

Chemical Abstract Service (CAS) Registry Number: 186826-86-8, 151096-09-2 (base)

Molecular Weight: 437.9, 401.4 (base)

The qualitative and quantitative composition of the proposed Moxifloxacin AF ophthalmic solution drug product is shown in Table 2.1.1-1.

Table 2.1.1-1 Composition of Moxifloxacin AF Ophthalmic Solution 0.5%

Component	Quality Standard	Function	%, w/v
Moxifloxacin Hydrochloride	Non-compendial[a]	Active ingredient	0.545%[b]
Xanthan Gum	NF	(b) (4)	
Sodium Chloride	USP	(b) (4)	
Boric Acid	NF	(b) (4)	
Sorbitol	NF	(b) (4)	
Tyloxapol	USP	(b) (4)	
Hydrochloric Acid and/or Sodium hydroxide	NF	pH adjustment	Adjust pH to 7.4
Purified Water	USP	(b) (4)	(b) (4)

[a] Although moxifloxacin hydrochloride has a Ph. Eur. Monograph, the Applicant will continue to test the material to the specifications approved for VIGAMOX® (NDA 21-598).
[b] 0.545% moxifloxacin hydrochloride is equivalent to 0.5% moxifloxacin base.

Source: Original NDA 22-428, Section 2.3.P

The formulation used in clinical studies is the same as the one intended for marketing (Formulation ID No. 107022). The Moxifloxacin AF formulation contains the same active ingredient and is proposed for the same indication as the previously approved VIGAMOX®, however the formulation has been modified to enhance retention on the eye. It contains a xanthan gum (b) (4) of the product on the ocular surface versus VIGAMOX®. A comparison of the qualitative and quantitative composition of the proposed Moxifloxacin AF ophthalmic solution drug product versus VIGAMOX® is presented in Table 2.1.1-2.

Table 2.1.1-2 Comparative Composition of Moxifloxacin AF and VIGAMOX®

Component	% Composition in Formulation	
	Moxifloxacin AF	VIGAMOX®
Moxifloxacin Hydrochloride	0.545%	0.545%
Xanthan Gum	(b) (4)	
Sodium Chloride	(b) (4)	(b) (4)
Boric Acid	(b) (4)	
Sorbitol	(b) (4)	
Tyloxapol	(b) (4)	
Hydrochloric Acid and/or Sodium hydroxide	Adjust pH to 7.4	Adjust pH to 6.8
Purified Water	(b) (4)	

Source: Original NDA 22-428, Section 2.3.P

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Moxifloxacin is a fluoroquinolone antibiotic that inhibits bacterial DNA synthesis via enzymatic inhibition of DNA gyrase and topoisomerase IV, ultimately resulting in bacterial cell death. 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. Moxifloxacin AF is proposed for the treatment of bacterial conjunctivitis.

2.1.3. What is the proposed dosage and route of administration?

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.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

Pursuant to the FDA's Complete Response letter for the original NDA 22-428, a prospective, randomized, vehicle-controlled, double-masked confirmatory efficacy and safety trial was conducted (Study C-07-40), in which patients with bacterial conjunctivitis received moxifloxacin AF or placebo administered as one drop BID in both eyes for 3 days. In addition, a clinical pharmacology study investigating moxifloxacin concentrations in conjunctival tissue and aqueous humor following administration of single doses of Moxifloxacin AF and VIGAMOX in cataract patients (Study C-07-12) was conducted. Study C-07-12 was a single-dose, double-masked, randomized, parallel group study in 130 patients who required cataract surgery. Patients were randomized to receive Moxifloxacin AF Ophthalmic Solution (n = 65) or VIGAMOX (n = 65) and assigned to a sample collection time point (0.25, 0.5, 1, 3, or 5 hours post-dose) for determination of conjunctiva and aqueous humor concentrations.

2.2.2. What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

As agreed upon with the FDA (IND 59,944, SN0116 dated 29APR2008: Special Protocol Assessment (SPA); FDA comments dated 04JUN2008), the primary efficacy endpoint was clinical cure in the microbiological intent to treat (MBITT) population at the Day 4 end of therapy (EOT) visit. Clinical cure was attained if the sum of the two cardinal ocular signs of bacterial conjunctivitis (bulbar conjunctival injection and conjunctival discharge/exudate) was zero (ie, normal or absent). These signs were rated on a standardized 4-point scale (normal/absent = 0; mild = 1; moderate = 2; and severe = 3).

2.2.3. Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety moxifloxacin was appropriately identified and measured in conjunctival tissue and aqueous humor for purposes of describing concentrations in anterior tissues of the eye following ocular administration by a validated ultra performance liquid chromatographic (UPLC) method with fluorescence detection.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Based on the applicant's analysis of Study C-07-40, Moxifloxacin AF administered BID for three days was superior to vehicle for clinical cure clinical cure at the Day 4 (EOT) visit (p = 0.0005,

MBITT dataset). Clinical cure rates were 62.5% and 50.6% for Moxifloxacin AF and vehicle, respectively. A formal exposure/dose-response analysis for efficacy could not be conducted since only a single strength/dose of active treatment was studied and no assessment of local or systemic concentrations of active drug were performed. For further discussion of the efficacy results and the adequacy of this resubmission in addressing the issues outlined in the Complete Response, refer to the Medical Officer's and Biostatistician's reviews of this application.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

In Study C-07-40, there were no clinically relevant differences in the adverse event profiles for patients receiving Moxifloxacin AF BID for three days versus vehicle. The adverse event incidence rates were 1.5% (9/593) and 0.9% (5/586) for Moxifloxacin AF and vehicle, respectively. A summary of adverse events reported in this superiority study are presented in Table 2.2.4.2-1.

Table 2.2.4.2-1. Treatment-Related Adverse Events Reported in Study C-07-40

Adverse Event	Moxifloxacin AF (N = 593)		VIGAMOX® (N = 586)	
	N	%	N	%
Nervous System Disorders				
Headache	1	0.2	0	0
Eye Disorders				
Eye Irritation	4	0.7	3	0.5
Eye Pain	3	0.5	2	0.3
Eye Pruritis	1	0.2	0	0
Ocular Hyperaemia	1	0.2	0	0
Vision Blurred	0	0	1	0.2
Asthenopia	0	0	1	0.3

Source: 2.5.5 Overview of Safety

A formal exposure/dose-response analysis for safety could not be conducted since only a single strength/dose of active treatment was studied and no assessment of local or systemic concentrations of active drug were performed. For further discussion of the safety results and the adequacy of this resubmission in addressing the issues outlined in the Complete Response, refer to the Medical Officer's and Biostatistician's reviews of this application.

2.2.5. What are the PK characteristics of the drug and its major metabolite?

The extent of systemic exposure to moxifloxacin following topical ophthalmic administration of Moxifloxacin AF was evaluated in one multiple-dose pharmacokinetic (PK) study in healthy adults (Study C-05-15). This study was submitted in the original NDA submission for Moxifloxacin AF Ophthalmic Solution dated December 15, 2008. Refer to the Office of Clinical Pharmacology review of the original NDA submission (dated July 15, 2009) for an assessment of the systemic exposure data from this study.

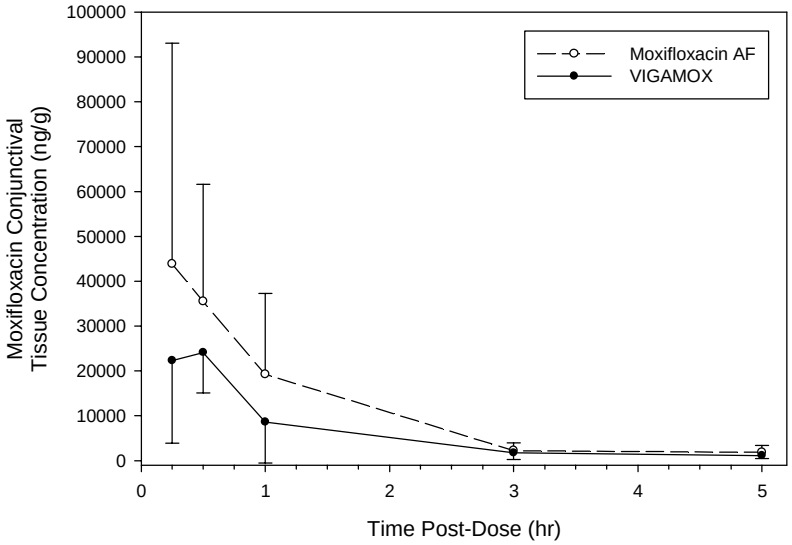
The current submission includes a clinical pharmacology study investigating moxifloxacin concentrations in conjunctival tissue and aqueous humor following administration of single doses of Moxifloxacin AF and VIGAMOX in cataract patients (Study C-07-12). Study C-07-12 was a single-dose, double-masked, randomized, parallel group study in 130 patients who required

cataract surgery. Patients were randomized to receive Moxifloxacin AF Ophthalmic Solution (n = 65) or VIGAMOX (n = 65) and assigned to a sample collection time point (0.25, 0.5, 1, 3, or 5 hours post-dose; planned randomization was equal across all time points in each treatment). Prior to cataract surgery, patients were administered one drop of study medication in the operative eye. Cataract surgery began at the assigned post-dose time point. At the initiation of surgery, two conjunctival biopsies and approximately 100 to 150 µL of aqueous humor was collected by paracentesis.

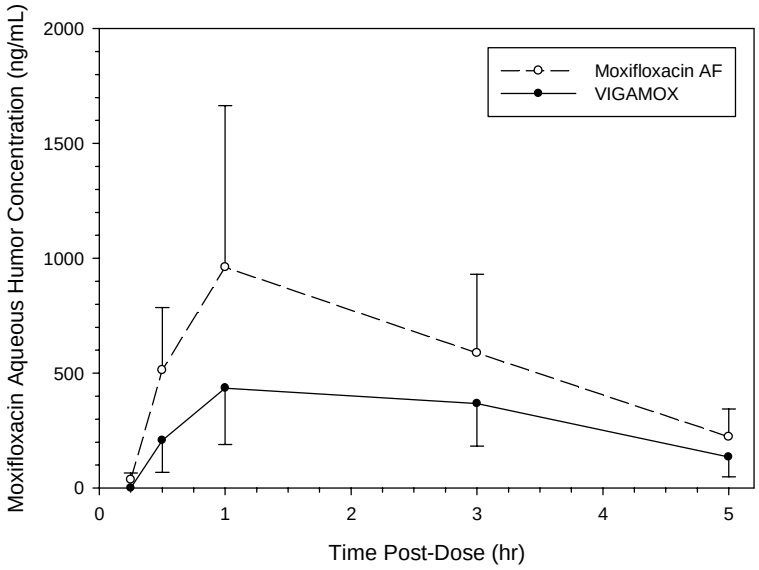
Concentration-time profiles for moxifloxacin in conjunctival tissue and aqueous humor following a single dose of Moxifloxacin AF and VIGAMOX in cataract patients are presented in Figure 2.2.5-1. Sparse sampling conjunctival and aqueous humor pharmacokinetic parameters for moxifloxacin following both treatments are summarized in Table 2.2.5-1. The sparse sampling AUC_{0-3} and AUC_{0-5} were significantly greater in conjunctival tissue and aqueous humor from patients administered Moxifloxacin AF relative to those from patients treated with VIGAMOX ($p = 0.0115$ and $p = 0.0006$, respectively). Although this study demonstrated that moxifloxacin concentrations in the anterior segment tissues of the eye after topical ocular administration of Moxifloxacin AF Ophthalmic Solution are higher than those following administration of VIGAMOX, the clinical relevance of these differences in in the treatment of bacterial conjunctivitis is unknown.

Figure 2.2.5-1. Mean Concentration-Time Profiles for Moxifloxacin in Conjunctival Tissue and Aqueous Humor Following Single Doses of Moxifloxacin AF and VIGAMOX in Cataract Patients

Conjunctival Tissue



Aqueous Humor



Source: C-07-12 Study Report, Tables 11.4.1.1.1-1 and 11.4.1.1.1-2

Table 2.2.5-1. Summary of Sparse Sampling Pharmacokinetic Parameters for Moxifloxacin in Conjunctival Tissue and Aqueous Humor Following Single Doses of Moxifloxacin AF and VIGAMOX in Cataract Patients

Treatment	Mean Cmax (ng/g)	Mean Tmax (hr)	AUC Estimates (ng·hr/g)			
			AUC*	SE	Lower 95% CI	Upper 95% CI
Conjunctival Tissue						
Moxifloxacin AF	43820	0.25	50548	7484	35225	65872
VIGAMOX	24112	0.50	27084	4821	17014	37154
Aqueous Humor						
Moxifloxacin AF	961	1	2801	313	2155	3446
VIGAMOX	435	1	1499	137	1217	1781

* Due to the limited number of quantifiable concentrations at 5 hours post-dose for the conjunctival tissue analysis, statistical comparison was made for AUC_{0-3}. Otherwise, the comparison was made for AUC_{0-5} for aqueous humor (per protocol).

Source: C-07-12 Study Report, Table 11.4.1.1.1-1 and 11.4.1.1.2-2

2.3. Intrinsic Factors

Not applicable.

2.4. Extrinsic Factors

Not applicable.

2.5. General Biopharmaceutics

Not applicable.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Conjunctiva and aqueous humor concentrations of moxifloxacin were identified and measured by an ultra performance liquid chromatographic (UPLC) method with fluorescence detection.

2.6.2. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total moxifloxacin concentrations were measured in conjunctiva and aqueous humor in Study C-07-12. The measurement of total concentrations of moxifloxacin in these matrices is appropriate.

2.6.3. What bioanalytical methods are used to assess concentrations?

Conjunctiva and aqueous humor concentrations of moxifloxacin were determined by an ultra performance liquid chromatographic (UPLC) method with fluorescence detection.

2.6.3.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Rabbit conjunctiva and aqueous humor were used for calibration. The calibration curve ranged from 10 to 1500 ng/sample for moxifloxacin in rabbit conjunctiva. The calibration curve ranged from 25 to 7500 ng/mL for moxifloxacin in rabbit aqueous humor. Calibration data were fitted to a linear model.

In general, the range of the assay was sufficient to measure moxifloxacin concentrations in aqueous humor for the intended purpose of describing concentrations in the anterior chamber of the eye following topical ocular administration.

A determination of the sufficiency of the assay to measure moxifloxacin concentrations in human conjunctiva could not be made. Conjunctival concentrations of moxifloxacin were reported as ng/sample for the standard curve in the validation report. For clinical samples, the amount of moxifloxacin determined in the biopsy samples was divided by the tissue weight to obtain the final moxifloxacin concentration (ng/g) for that sample. The relationship between the concentration units reported for validation (ng/sample) and the units reported for individual concentrations (ng/g) was not specified. Thus, the magnitude of moxifloxacin concentrations from the clinical samples (in ng/g) could not be compared to the range of concentrations in the standard curve (in ng/sample). Because the sufficiency of the assay in measuring moxifloxacin concentrations in conjunctiva could not fully be evaluated, these study results should be used for informational purposes only.

2.6.3.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower limits of quantitation for moxifloxacin are10 ng/sample in conjunctiva and 25 ng/mL in aqueous humor. The upper limits of quantitation are 1500 ng/sample and 7500 ng/mL in conjunctiva and aqueous humor, respectively.

2.6.3.3. What are the accuracy, precision, and selectivity at these limits?

Accuracy and precision ranges for the assay of moxifloxacin in rabbit conjunctiva ranged from 95.5 to 103% of nominal and 1.46 to 4.44% RSD, respectively. Accuracy and precision ranges for the assay of moxifloxacin in rabbit aqueous humor ranged from 95.07 to 106% of nominal and 1.04 to 4.21% RSD, respectively. Selectivity against endogenous interferences was not reported.

2.6.3.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Results of sample stability studies were not reported.

2.6.3.5. What is the QC sample plan?

Each analytical run included QC standards conducted in at least duplicate at each of three concentrations as follows: 30.0 (low), 600 (medium), and 1200 (high) ng/sample concentrations in conjunctiva and 75.0 (low), 3000 (medium), and 6000 (high) ng/mL concentrations in aqueous humor.

For run acceptance, at least three-fourths of the individual calibration standards had to yield back-calculated concentrations within ± 15% of nominal (± 20 % at the lower limit of quantitation) and two-thirds of the QC samples had to assay within ± 15% of nominal with at least one QC at each concentration meeting this criterion.

3. LABELING RECOMMENDATIONS

No new labeling statements relating to section 12 CLINICAL PHARMACOLOGY were proposed in this Class 2 resubmission. For Clinical Pharmacology labeling recommendations, refer to the Office of Clinical Pharmacology review of the original NDA (dated July 15, 2009).

4. APPENDICES

4.1. Individual Study Reviews

4.1.1. Study C-07-12

TITLE:
A Double-Masked, Parallel Group, Pharmacokinetic Study of Moxifloxacin Concentrations in the Conjunctiva and Aqueous Humor After Single Topical Ocular Administration of Moxifloxacin AF Ophthalmic Solution 0.5% or VIGAMOX in Cataract Surgery Patients

Study Initiation:	24NOV2008
Study Completion:	19JAN2009
Investigator/Site:	Andrew Cottingham, MD, South Texas Eye Institute

OBJECTIVES:
To describe the concentrations of moxifloxacin in the conjunctiva and aqueous humor of cataract surgery patients after topical ocular administration of Moxifloxacin Alternative Formula (AF) Ophthalmic Solution 0.5% or VIGAMOX.

STUDY DESIGN:
This was a single-dose, double-masked, randomized, parallel group study in 130 patients who required cataract surgery. Patients were randomized to receive Moxifloxacin AF Ophthalmic Solution (n = 65) or VIGAMOX (n = 65) and assigned to a sample collection time point (0.25, 0.5, 1, 3, or 5 hours post-dose; planned randomization was equal across all time points in each treatment). Prior to cataract surgery, patients were administered one drop of study medication in the operative eye. Cataract surgery began at the assigned post-dose time point. At the initiation of surgery, two conjunctival biopsies and approximately 100 to 150 µL of aqueous humor was collected by paracentesis.

FORMULATIONS:
Test Product: Moxifloxacin AF Ophthalmic Solution 0.5%; batch number (Formulation Identification Number [FID] number), 08-500947-1 (107022)

Reference Product: Moxifloxacin Hydrochloride Ophthalmic Solution 0.5% (VIGAMOX); batch number (FID number), 08-500979-1 (101149)

PHARMACOKINETIC ASSESSMENTS:
Conjunctiva and aqueous humor samples for determination of moxifloxacin concentrations were collected by randomized sparse sampling at the following time points: 0.25 (± 5 min), 0.5 (± 5 min), 1 (± 10 min), 3 (± 15 min), or 5 (± 20 min) hours post-dose.

BIOANALYTICAL METHODOLOGY:
Conjunctiva and aqueous humor concentrations of moxifloxacin were determined via a validated fluorescence ultra pressure liquid chromatographic (UPLC) method. The working range of this assay was 10 to 1500 ng/sample and 25 to 7500 ng/mL for conjunctiva and aqueous humor, respectively. Sample analysis was completed in four analytical runs (two runs per matrix). All runs met acceptance criteria and no repeat analyses were required. Accuracy and precision for the assay of concentrations in human conjunctiva ranged between 93.33% to 100.83% and 1.55 to

6.57% RSD, respectively. Accuracy and precision for the assay of concentrations in human aqueous humor ranged between 93.47% to 103.00% and 1.91 to 6.18% RSD, respectively.

The amount of moxifloxacin determined in the two conjunctival biopsy samples was divided by the tissue weight to obtain the final moxifloxacin concentration (ng/g) for that sample. Moxifloxacin concentrations or amounts that were below the assay limit of quantitation in the conjunctival tissue (< 10 ng) or in the aqueous humor (< 25 ng/mL) were assigned one-half the quantitation limit in the statistical and PK analyses.

Reviewer Comment: Conjunctival concentrations of moxifloxacin were reported as ng/sample for the standard curve in the validation report. For clinical samples, the amount of moxifloxacin determined in the biopsy samples was divided by the tissue weight to obtain the final moxifloxacin concentration (ng/g) for that sample. The relationship between the concentration units reported for validation (ng/sample) and the units reported for individual concentrations (ng/g) was not specified. Thus, the magnitude of moxifloxacin concentrations from the clinical samples (in ng/g) could not be compared to the range of concentrations in the standard curve (in ng/sample).

PHARMACOKINETIC/STATISTICAL ANALYSIS:
The primary pharmacokinetic (PK) variable was area under the concentration-time curve (AUC) up to the last measured concentration (i.e. AUC_{0-5}). AUC calculations were based on mean conjunctival and aqueous humor drug concentrations of moxifloxacin at each of the five sparse sampling time points. AUC for each time point and treatment group was estimated using a method appropriate for sparse sampling. For each time point, a test for equality between treatment AUCs was constructed in the form of contrasts and a 95% confidence interval for the difference in AUCs was estimated.

Reviewer Comment: The standard deviations for AUC values was not reported and the method by which the applicant calculated 95% confidence intervals for the primary parameter AUC (i.e. boot-strapping, etc.) is not clear.

The maximum mean concentration (Cmax) and the time point at which the Cmax was observed (Tmax) were also estimated as secondary parameters.

Reviewer Comment: The Cmax reported in Study C-07-12 was not a 'true' Cmax. In this study, Cmax was defined as the maximal mean concentration based on the mean concentration values for each time point, in contrast to a mean of the actual observed maximum concentrations per patient.

Patients with samples collected outside the specified time windows were still included at each nominal time point, as the variance in the actual versus nominal times was minimal (6 minutes or less) and not expected to impact PK assessments.

RESULTS:
Study Population
Of the 130 cataract patients enrolled in this study, all received test article and all were evaluable for safety analysis. Three patients were excluded from the overall PK analysis for the following reasons: one patient received test article but was discontinued due to the patient's decision unrelated to an adverse event, prior to the collection of conjunctival and aqueous humor samples; one patient was administered an excluded concomitant medication preoperatively; and one patient had their aqueous humor sample lost during processing and their conjunctival sample was not rinsed per protocol.

Of the 127 patients evaluable for overall PK analysis, two additional patients were excluded from the PK dataset for aqueous humor analysis due either to the sample being lost during processing or the sample being diluted upon collection. In addition, five patients had very low (< 0.1 mg) conjunctival tissue weights (#3103, 0.25 hr, VIGAMOX; #3104, 0.25 hr, Moxifloxacin AF; #3203, 0.5 hr, VIGAMOX; #3403, 3.0 hr, Moxifloxacin AF; and #5204, 0.5 hr, VIGAMOX). The PK analysis of the conjunctival tissue data was performed including and excluding these five patients with low sample weights. In three patients it was also noted that aqueous humor samples were hemolyzed upon receipt. The bioanalytical method for aqueous humor showed no interference in the presence of hemolysis, thus these samples were included in the analysis.

Demographics

A summary of demographic and baseline characteristics for the pharmacokinetic population is presented in Table 1. There were no relevant differences in demographic characteristics between the treatment groups.

Table 1. Demographics and Baseline Characteristics – Pharmacokinetic Population

Treatment	N	Age* (yr)	Sex N (%)	Race N (%)	Iris Color N (%)
Moxifloxacin AF	63	70 (40 – 88)	23 (36.5) Male 40 (63.5) Female	60 (95.2) White 3 (4.8) Black or African American	32 (50.8) Brown 8 (12.7) Hazel 2 (3.2) Green 21 (33.3) Blue
VIGAMOX	64	71 (39 – 90)	31 (48.4) Male 33 (51.6) Female	61 (95.3) White 2 (3.1) Black or African American 1 (1.6) Asian	34 (53.1) Brown 9 (14.1) Hazel 6 (9.4) Green 15 (23.4) Blue

*Data presented as mean (range).
Source: C-07-12 Study Report, Section 11.2.1.1

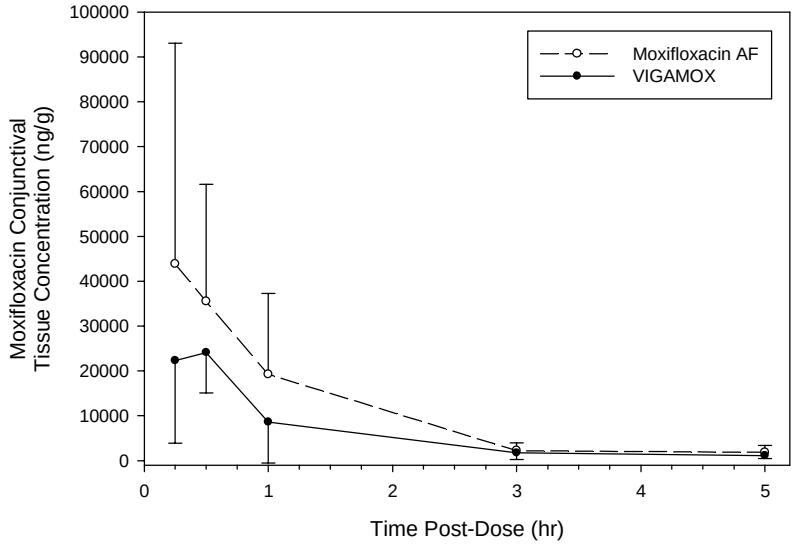
Moxifloxacin Concentrations in Conjunctival Tissue

Concentration-time profiles for moxifloxacin in conjuctival tissue following a single dose of Moxifloxacin AF and VIGAMOX in cataract patients are presented in Figure 1. Measurable moxifloxacin concentrations in conjunctival tissue were achieved by the first collection time point (15 min) after single topical ocular instillation of each treatment. Quantifiable amounts (b) (4) of moxifloxacin were measured in conjunctival tissue homogenates in 6 of 13 patients receiving Moxifloxacin AF and 5 of 13 patients receiving VIGAMOX at 3 hours post-dose. At 5 hours post-dose, quantifiable moxifloxacin amounts in the conjunctival tissue homogenates were only found in 3 or 11 patients in the Moxifloxacin AF group and in no patients in the VIGAMOX group.

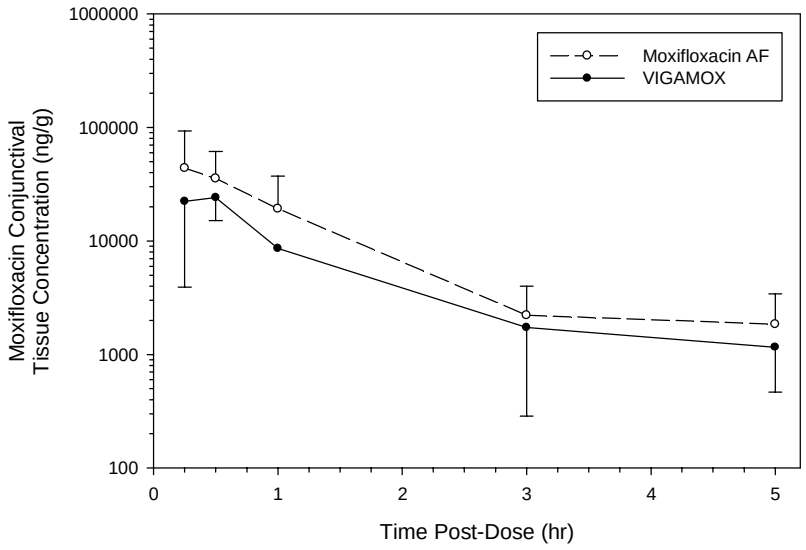
Sparse sampling conjunctival tissue PK parameters for both treatment groups are presented in Table 1. The time point with the maximum mean concentration was defined as Tmax and the mean concentration at that time point was considered Cmax. Due to the limited number of quantifiable concentrations at 5 hours post-dose, statistical comparison was made for AUC_{0-3}. The sparse sampling AUC_{0-3} was significantly greater in conjunctival tissue from patients administered Moxifloxacin AF relative to that from patients treated with VIGAMOX ($p = 0.0115$).

Figure 1. Mean Concentration-Time Profiles for Moxifloxacin in Conjunctival Tissue Following Single Doses of Moxifloxacin AF and VIGAMOX in Cataract Patients (Linear and Logarithmic Scales)

Linear Scale



Logarithmic Scale



Source: C-07-12 Study Report, Table 11.4.1.1.1-1

Table 1. Summary of Sparse Sampling Pharmacokinetic Parameters for Moxifloxacin in Conjunctival Tissue Following Single Doses of Moxifloxacin AF and VIGAMOX in Cataract Patients

Treatment	Mean Cmax (ng/g)	Mean Tmax (hr)	AUC_{0-3} Estimates (ng·hr/g)			
			AUC_{0-3}	SE	Lower 95% CI	Upper 95% CI
Moxifloxacin AF	43820	0.25	50548	7484	35225	65872
VIGAMOX	24112	0.50	27084	4821	17014	37154

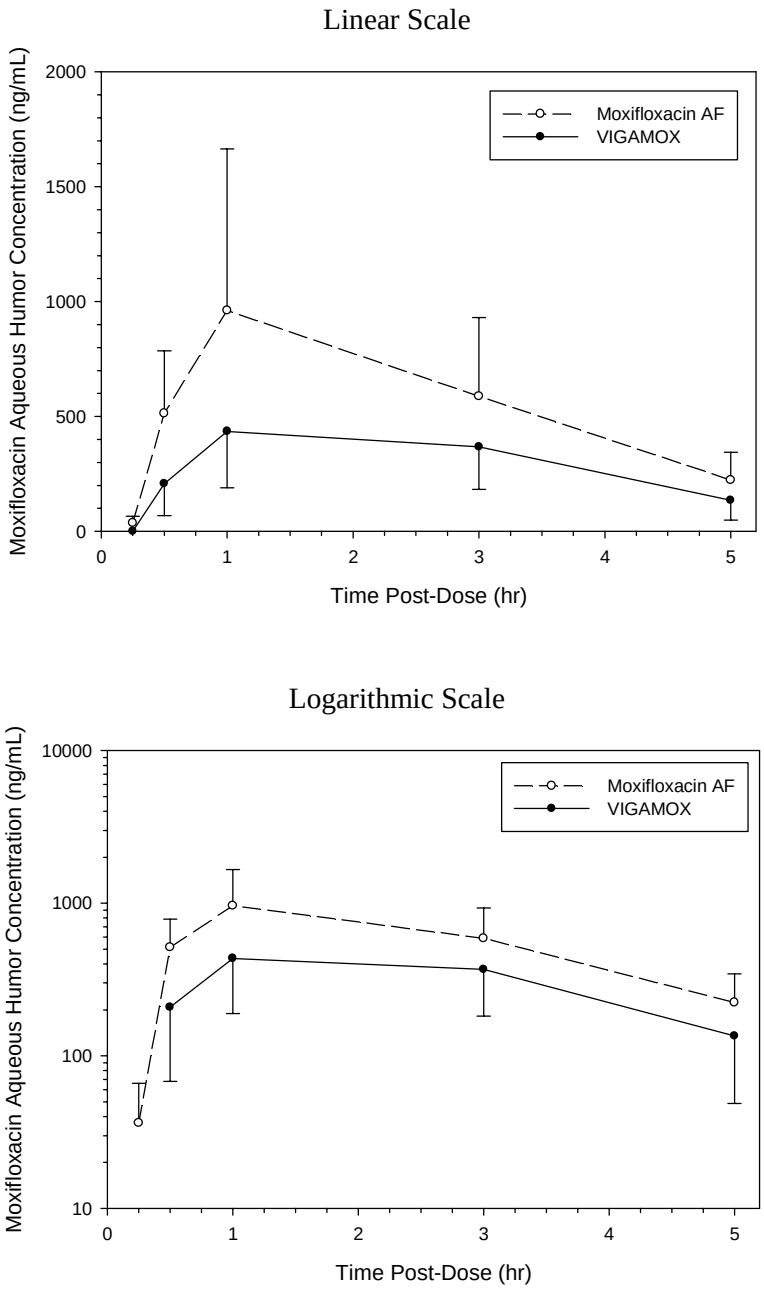
Source: C-07-12 Study Report, Table 11.4.1.1.1-1

Moxifloxacin Concentrations in Aqueous Humor

Concentration-time profiles for moxifloxacin in aqueous humor following a single dose of Moxifloxacin AF and VIGAMOX in cataract patients are presented in Figure 2. Quantifiable moxifloxacin concentrations in aqueous humor were observed by the first collection time point (15 min) after single topical ocular instillation in 6 of 13 patients receiving Moxifloxacin AF and 3 of 13 patients receiving VIGAMOX. Moxifloxacin concentrations were quantifiable in aqueous humor samples at 5 hours in the majority of patients in both treatment groups (10 of 13 for Moxifloxacin AF and 12 of 13 for VIGAMOX).

Sparse sampling aqueous humor PK parameters for both treatment groups are presented in Table 2. The sparse sampling AUC_{0-5} was significantly greater in aqueous humor from patients administered Moxifloxacin AF relative to that from patients treated with VIGAMOX ($p = 0.0006$).

Figure 1. Mean Concentration-Time Profiles for Moxifloxacin in Aqueous Humor Following Single Doses of Moxifloxacin AF and VIGAMOX in Cataract Patients (Linear and Logarithmic Scales)



Source: C-07-12 Study Report, Table 11.4.1.1.1-2

Table 2. Summary of Sparse Sampling Pharmacokinetic Parameters for Moxifloxacin in Aqueous Humor Following Single Doses of Moxifloxacin AF and VIGAMOX in Cataract Patients

Treatment	Mean Cmax (ng/g)	Mean Tmax (hr)	AUC_{0-5} Estimates (ng·hr/g)			
			AUC_{0-5}	SE	Lower 95% CI	Upper 95% CI
Moxifloxacin AF	961	1	2801	313	2155	3446
VIGAMOX	435	1	1499	137	1217	1781

Source: C-07-12 Study Report, Table 11.4.1.1.2-2

SPONSOR'S CONCLUSIONS:
This study demonstrated that moxifloxacin concentrations in the anterior segment tissues of the eye (e.g. conjunctiva) after topical ocular administration of Moxifloxacin AF Ophthalmic Solution are higher than those following administration of VIGAMOX.

REVIEWER ASSESSMENT:
Results from Study C-07-12 adequately described the concentrations of moxifloxacin in the conjunctiva and aqueous humor of cataract surgery patients after topical ocular administration of Moxifloxacin Alternative Formula (AF) Ophthalmic Solution 0.5% or VIGAMOX. In general, the Applicant's pharmacokinetic conclusions based on these findings are acceptable from a Clinical Pharmacology perspective. The clinical relevance of conjunctiva and aqueous humor concentrations to the proposed clinical indication has not been demonstrated. In addition, the sufficiency of the assay in measuring moxifloxacin concentrations in conjunctiva could not fully be evaluated. Thus, findings from Study C-07-12 have limited utility at this stage of development.

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

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/s/

KIMBERLY L BERGMAN
08/20/2010

CHARLES R BONAPACE
08/20/2010