

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-598

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

**OFFICE OF CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW**

NDA (21-598)	Submission Date(s): 10/15/2002; 12/13/2002
Brand Name	TBD
Generic Name	Moxifloxacin
Reviewer	Lei Zhang, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm. D.
OCPB Division	DPE III (HFD-880)
ORM division	DAAODP (HFD-550)
Sponsor	Alcon, Inc.
Relevant IND(s)	_____
Submission Type; Code	3;P (3;S)
Formulation; Strength(s)	0.5% Ophthalmic Solution
Indication	Treatment of Bacterial Conjunctivitis _____

1 Executive Summary

Moxifloxacin HCl is a fourth generation quinolone developed by Bayer AG. Moxifloxacin tablet (400 mg) and IV (400 mg/250 mL) formulations were approved in multiple countries including the United States (NDA 21-085, NDA 21-277 and NDA 21-334) for the treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis and uncomplicated skin and skin structure infections. Moxifloxacin HCl exhibits rapid bactericidal activity against both Gram-positive and Gram-negative bacterial pathogens. Moxifloxacin also has superior activity compared to ciprofloxacin against quinolone resistant strains of *Staphylococcus aureus* and other Gram-positive pathogens.

Bacterial conjunctivitis in children is predominantly caused by *H. influenzae* and *S. pneumoniae*. On the basis of its reported activity against *S. aureus*, *H. influenzae* and *S. pneumoniae*, it was reasoned that moxifloxacin HCl would be effective for treating bacterial infections of the eye. In adults, in addition to *H. influenzae* and *S. pneumoniae*, there is a wider diversity of Gram-positive and Gram-negative pathogens associated with bacterial conjunctivitis. The sponsor, Alcon, has developed _____ formulation, Moxifloxacin Ophthalmic Solution, 0.5% (Moxifloxacin 0.5%) for the treatment of bacterial conjunctivitis in both pediatric and adult patients and _____ and NDA 21-598 (for adult patients) for this product.

The product is intended to be applied topically to the eye for local therapeutic effect (anti-infective). Although eye is the effective site, it is not possible to measure the ocular concentrations (biological-relevant concentrations) of moxifloxacin in humans by standard methods. To support the Human Pharmacokinetics and Bioavailability section of this NDA, the sponsor provided the results of a multiple dose pharmacokinetics study (Study No. C-01-48) in healthy adult subjects. In this study, the systemic exposure of moxifloxacin was determined following three times daily administration of Moxifloxacin 0.5% (one drop per eye) for four days with one additional dose on Day 5 in 21 healthy subjects. After the first topical ocular dose of moxifloxacin 0.5% ophthalmic solution, mean C_{max} was 1.2 ± 0.8 ng/mL. Following topical ocular dosing three times per day for four days, the mean steady-state peak plasma concentrations of moxifloxacin (Day 5) was 2.7 ± 1.3 ng/mL. This level of exposure is approximately 1600-times lower than the mean C_{max} reported (4.5 µg/mL) after well tolerated therapeutic oral dose of 400 mg. The estimated daily $AUC_{0-\infty}$ following topical administration to steady-state was 45 ng•h/mL, which is approximately 1000-times lower than the value reported after the recommended 400 mg oral dose (48 µg•h/mL). The estimated half-life of 13.1 ± 3.3 hours was similar to that reported in healthy subjects after oral and IV dosing. Maximum plasma concentrations and area under the plasma concentration-time curve were slightly higher in females than in the males; however, when normalized to body weight, the differences decreased. The pharmacokinetic parameters for Caucasian and Asian subjects were similar.

1.1 Comments to the CMC-Microbiology Reviewer

It is not clear how the current formulation (with sodium chloride, boric acid and purified water, and hydrochloric acid or sodium hydroxide to adjust pH to 6.8) makes this product

1.2 Comments to the Medical Officer

To avoid potential interactions with other commonly prescribed ophthalmic solution products that patients may apply at the same time (e.g., ophthalmic solutions for the treatment of glaucoma) due to its topical ocular route, please add a statement to the PRECAUTIONS SECTION stating that

1.3 Comments to the Sponsor

Please convey the following comments to the sponsor:

1. While not an impediment to approval, the agency is still awaiting the updated information regarding long-term frozen storage stability of moxifloxacin in human plasma to cover the time period between initiation of these studies and completion of sample analysis.
2. The agency does not agree with the approach to replace below the LOQ (BLQ) values with one half of the LOQ for calculating the mean values for data analysis. In the

future, please replace BLQ levels with zero and calculate both mean of all data and mean of measurable values.

1.4 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the _____ NDA-21-598 submitted on Oct 15, 2002. The Human Pharmacokinetics and Bioavailability Section of this submission(s) for Moxifloxacin 0.5% Ophthalmic Solution has been found to be acceptable for meeting the OCPB requirements. Recommendations for consideration for the final labeling were included in Section 5 (Labeling, Pages 12-13).

Lei Zhang, Ph.D. _____
PK Reviewer, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Dennis Bashaw, Pharm.D. _____
Team Leader, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

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3 Summary of Clinical Pharmacology and Biopharmaceutis Findings

The proposed product, (moxifloxacin HCl ophthalmic solution) 0.5%, sterile topical ophthalmic solution formulated with sodium chloride, boric acid and purified water. It may also contain hydrochloric acid/sodium hydroxide to adjust pH. The solution is isotonic and formulated at pH 6.8 with an osmolality of approximately — Each mL of the product solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.

The product is intended to be applied topically to the eye for local therapeutic effect (anti-infective). Although eye is the effective site, it is not possible to measure the ocular concentrations (biological-relevant concentrations) of moxifloxacin in humans by standard methods. To support the Human Pharmacokinetics and Bioavailability section of this NDA, the sponsor provided study reports on three studies all conducted in healthy adult subjects by measuring systemic moxifloxacin levels and moxifloxacin levels in tears:

1. Study C-01-16:
A Fifteen-Day, Double-Masked, Randomized, Multiple-Dose Safety/Pharmacokinetic Study of Moxifloxacin Ophthalmic Solution Following Topical Ocular Administration in Normal, Healthy Male Japanese and Caucasian Subjects
2. Study C-01-48:
An Open-Label, Single Center, Multiple-Dose Pharmacokinetic Study of Moxifloxacin Ophthalmic Solution 0.5% Following Topical Ocular Administration in Healthy Male and Female Adult Volunteers
3. Study C-01-53:
An Open-Label, Multiple-Dose Study of the Safety and Tear Film Pharmacokinetics of Moxifloxacin Ophthalmic Solution Following Topical Ocular Administration in Healthy Volunteers

The multiple dose pharmacokinetics studies (Studies C-01-48 and C-01-16) have been reviewed in detail (see Appendix 6.2.1 and 6.2.2). The systemic exposure and PK parameter information were obtained from Study C-01-48 and were cited in the labeling. Study C-01-53 was not reviewed because the information obtained was not used to construct labeling information. A brief review indicated that there was considerable inter-subject variability in tear concentrations at each collection time and there were frequent samples that were not quantifiable. Although the area under the inhibitory curve (AUC) derived from tear concentration-time curve against different minimum inhibitory concentration (MIC) values for different bacterial isolates may be used to predict/correlate with clinical response in patients with external ocular infection, exposure and clinical outcomes were not measured in the same patients in this application.

Moxifloxacin levels in plasma were quantified by the validated HPLC methods with fluorescent detection. The assay method was acceptable in regards to sensitivity and selectivity. Long-term frozen storage stability assessment was in progress at the time of submission. The sponsor will be asked to provide updated information in terms of long-term frozen storage stability of moxifloxacin in human plasma to cover the time period

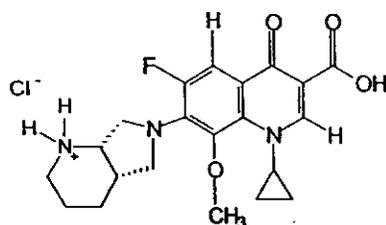
between initiation of these studies and completion of sample analysis (see Comments to the sponsor).

4 QBR

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of moxifloxacin, and the formulation of the drug product?

Moxifloxacin is a fourth-generation fluoroquinolone antibacterial agent active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens, atypical microorganisms and anaerobes.



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

Mol Wt 437.9

Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride. Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8 position, and an S,S- configured diazabicyclononyl ring moiety at the 7 position.

Moxifloxacin hydrochloride is a slightly yellow to yellow crystalline powder. The moxifloxacin HCl ophthalmic solution 0.5% is a sterile topical ophthalmic solution formulated at pH 6.8 with an osmolality of approximately

Table 4.1.1.1 Components of 0.5% Moxifloxacin Solution

Component	% w/v	Function
Moxifloxacin HCl	0.545	Active Ingredient
Sodium Chloride	—	—
Boric Acid	—	—
Sodium Hydroxide Hydrochloric Acid	pH Adjustments (final pH 6.8)	pH Adjusters
Purified Water	QS 100	—

4.1.2 What is its mechanism of action and therapeutic indication?

Targeting at both DNA gyrase and topoisomerase IV, moxifloxacin and other fluoroquinolone antimicrobials exert their antimicrobial activity by inhibiting bacterial

DNA synthesis and arresting bacterial cell growth and division by stabilizing the DNA-enzyme complex. Thereby, fluoroquinolones are bactericidal as well as bacteriostatic. Although both DNA gyrase and topoisomerase IV are targets of fluoroquinolones, the degree of targeting is organism-specific. In *Escherichia coli*, DNA gyrase is the primary and topoisomerase IV is the secondary enzymatic target. In contrast, topoisomerase IV is the primary drug target for *Staphylococcus aureus*. This difference in drug targeting has important implications with regard to the spectrum of activity and the potential for development of resistance. Moxifloxacin demonstrates excellent concentration-dependent bactericidal activity against a wide range of microorganisms including Gram-positive cocci, aerobic or intracellular bacteria, and "atypical" organisms such as *Mycoplasma*, *Mycobacterium* and *Chlamydia*. The C-8-methoxy moiety confers increased bactericidal activity against *S. aureus* and *Escherichia coli* including those strains that contain one-step mutation in topoisomerase II or IV. Moxifloxacin HCl exhibits rapid bactericidal activity against both Gram-positive and Gram-negative bacterial pathogens, including staphylococci, *Streptococcus pneumoniae*, members of the *Enterobacteriaceae* family, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, as well as atypical pathogens and anaerobes. Moxifloxacin also has superior activity compared to ciprofloxacin against quinolone resistant strains of *Staphylococcus aureus* and other Gram-positive pathogens.

Bacterial conjunctivitis in children is predominantly caused by *H. influenzae* and *S. pneumoniae*. On the basis of its reported activity against *S. aureus*, *H. influenzae* and *S. pneumoniae*, it was reasoned that moxifloxacin HCl would be effective for treating bacterial infections of the eye. In adults, in addition to *H. influenzae* and *S. pneumoniae*, there is a wider diversity of Gram-positive and Gram-negative pathogens associated with bacterial conjunctivitis. The therapeutic indication of moxifloxacin 0.5% solution is for the treatment of bacterial conjunctivitis in both pediatric and adult patients.

4.1.3 What is the proposed dosage and route of administration?

The proposed dosage is one drop in the affected eye 3 times a day by topical ocular administration.

4.1.4 What is known about moxifloxacin (background on the previously approved IV and oral product)?

Moxifloxacin HCl, an 8-methoxy-6-fluoroquinolone, is a fourth generation quinolone developed by Bayer AG. Moxifloxacin tablet (400 mg) and IV (400 mg/250 mL) formulations under the trade name Avelox were approved in multiple countries including the United States for the treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis and uncomplicated skin and skin structure infections.

Oral moxifloxacin is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin is approximately 90%. Co-administration with a high fat meal does not affect the absorption of moxifloxacin. Moxifloxacin is approximately 50% bound to serum proteins, independent of drug concentration. Approximately 45% of an oral or IV dose of moxifloxacin is excreted unchanged (~20% in urine and ~25% in

feces). The mean total body clearance and renal clearance are 12 ± 2 L/hr and 2.6 ± 0.2 L/hr, respectively. The volume of distribution ranges from 1.7 to 2.7 L/kg, and elimination plasma half-life of moxifloxacin is 12 ± 1.3 hr. Moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 is not involved in metabolism. *In vitro* studies with cytochrome P450 enzymes indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2.

Please refer to NDA 21-085, NDA 21-277 and NDA 21-334 for detailed information about moxifloxacin.

4.2 General Clinical Pharmacology

4.2.1 What are the clinical-response endpoints (i.e., clinical or surrogate endpoints or biomarkers) and how are they measured in clinical study? What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Efficacy variables: The primary clinical efficacy endpoints were 1) the clinical cure rate for bulbar conjunctival injection and conjunctival discharge/exudate (i.e., the two cardinal ocular signs of bacterial conjunctival infection) at Day 5, and 2) Microbiological cure, i.e., eradication of all pre-therapy pathogens at Day 6. Clinical cure was attained when the sum of the ratings for the two cardinal signs equaled zero (i.e., normal or absent) and was considered to be the only acceptable endpoint for this self-limiting ocular disorder. Secondary clinical efficacy variables included the individual ocular signs and symptoms (i.e., bulbar conjunctival injection, conjunctival discharge/exudate, lid erythema, lid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at each visit.

Safety Measures: Visual acuity, biomicroscopy, fundus exam, and incidence of adverse events.

Exposure Measures: The product is intended to be applied topically to the eye for local therapeutic effect (anti-infective). Although eye is the effective site, it is not possible to measure the ocular concentrations of moxifloxacin in humans by standard methods. In this submission, systemic exposure of moxifloxacin in plasma (non-relevant biological fluid) was determined and PK was evaluated in healthy subjects only. Therefore, exposure-response relationship for efficacy is not readily available.

In the PK studies, efficacy was not evaluated since the subjects were healthy normal, but safety profiles were obtained. No deaths or other serious adverse events were reported from studies. Adverse events were non-serious and almost all resolved without treatment and did not interrupt subject continuation in the study. No clinically relevant changes from baseline in general physical exam, cardiovascular parameters, ocular signs, visual acuity, etc. were observed. No safety issues were identified and no treatment related changes were observed based upon an evaluation of hematology, blood chemistry and urinalysis laboratory data.

4.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

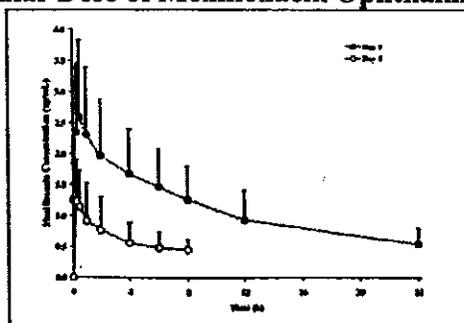
The active parent moiety, moxifloxacin, was appropriately identified and measured in the plasma. Please refer to the Bioanalytical Section (4.6).

4.2.3 What are the systemic exposures of moxifloxacin after topical ocular administration and how are they compared to exposures under standard therapeutic oral and IV doses?

Although ocular level of moxifloxacin could not be measured, systemic exposure of moxifloxacin in plasma was measured in Study C-01-48 (see Appendix 6.2.2 for details). A total of 21 adult healthy subject were enrolled. The subjects were applied one drop of test drug solution (0.5% moxifloxacin) in each eye 3 times daily (every 8 hours) for four days, with an additional dose on the morning of Day 5. After the first topical ocular dose of moxifloxacin 0.5% ophthalmic solution, plasma samples with quantifiable moxifloxacin concentrations (\geq ng/mL) were obtained in 16 of 21 subjects. The mean C_{\max} was 1.2 ± 0.8 ng/mL. Following topical ocular dosing three times per day for four days, all subjects has attained steady-state by Day 3 and quantifiable plasma concentrations of moxifloxacin were seen in all 21 subjects after the last dose on Day 5. The mean steady-state peak plasma concentrations of moxifloxacin (Day 5) was 2.7 ± 1.3 ng/mL. This level of exposure is approximately 1600-times lower than the mean C_{\max} reported ($4.5 \mu\text{g/mL}$) after well tolerated therapeutic oral dose of 400 mg. The estimated daily $\text{AUC}_{0-\infty}$ following topical administration to steady-state was $45 \text{ ng}\cdot\text{h/mL}$, which is approximately 1000-times lower than the value reported after the recommended 400 mg oral dose ($48 \mu\text{g}\cdot\text{h/mL}$). The estimated half-life of 13.1 ± 3.3 hours was similar to that reported in healthy subjects after oral and IV dosing.

The mean and range of steady-state peak plasma concentrations of moxifloxacin were generally higher on Day 5 compared to Day 1 (Figure 4.2.3.1). Accumulation ratios of moxifloxacin in plasma were estimated 3 ways: 1) observed individual C_{\max} on Day 5/ C_{\max} on Day 1; 2) estimated individual AUC_{0-8} on Day 5/ AUC_{0-8} on Day 1; and 3) based on terminal phase elimination rate constant (λ_z) and three times-a-day dosing. By these methods, the mean accumulation ratios were approximately 2.0, 2.5, and 2.9, respectively. The accumulation ratios by all 3 methods were comparable.

Figure 4.2.3.1. Mean \pm SD Moxifloxacin Plasma Profile Following the First and Last Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5%



4.2.4 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Only PK in plasma (non-biological relevant fluid) was determined in healthy subjects. We do not have any PK information in patients. Systemic exposure of moxifloxacin (C_{max} or AUC) in healthy subjects under the proposed dose regimen via topical ocular route is about 1000-times lower compared to the levels found to be safe under the standard oral dose therapy. Although overall metabolism of moxifloxacin is not expected to be different between healthy subjects and patients with conjunctivitis, inflammation of corneal tissues may enhance absorption of moxifloxacin, leading to higher exposure at effective sites in patients which may have implications on safety and efficacy.

4.3 Intrinsic Factors

4.3.1 Are there any effects of intrinsic factors (such as gender, renal impairment, hepatic impairment and ethnicity) influence exposure and/or response of moxifloxacin after topical ocular administration? What are the dose recommendations for special populations?

Because drug concentrations were measured from a non-relevant biological fluid (i.e., plasma), these intrinsic factors would not apply. The intrinsic factors have been studied in the Avelox application. No difference will be anticipated due to route of administration, therefore, many results from the Avelox application could be used as a guidance for this product.

Gender and Race:

From Study C-01-48, systemic exposure between genders and races (Caucasian and Asian) were compared (see Appendix 6.2.2 for details). The results obtained are consistent with what have been found for the oral Avelox, i.e., in terms of gender, C_{max} and AUC values were higher in females than in males and when normalized to body weight differences, the difference in C_{max} , and AUC values decreased. In terms of race, there were little differences in C_{max} and AUC. There are no dosage adjustment recommended with regards to gender and race.

Renal and hepatic impairment:

Based on the results in Avelox application and the low systemic exposure by the topical route of administration, no dosage adjustment of moxifloxacin solution is needed in patients with renal and hepatic impairment.

Age:

PK between elderly patients and young patients was similar following both oral and IV administration in previous studies. No dosage adjustment is needed based on age.

PK of moxifloxacin in pediatric subjects has not been studied. In this NDA, 0.5% moxifloxacin solution has been shown to be safe and effective in pediatric patients

There is no evidence that the ophthalmic administration of 0.5% moxifloxacin solution has any effect on weight bearing joints, even though oral

administration of some quinolones has been shown to cause arthropathy in immature animals.

Pregnant women or nursing mothers:

There are no adequate and well-controlled studies in pregnant women. Moxifloxacin solution could be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Moxifloxacin is excreted in the breast milk of rats. Although moxifloxacin has not been measured in human milk, it may also be excreted in human milk. Caution should be exercised when 0.5% moxifloxacin solution is administered to a nursing mother.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Drug-Drug Interaction:

While drug-drug interaction studies have not been conducted with 0.5% moxifloxacin solution, they have been performed with the oral product at much higher systemic exposures than are achieved by the topical ocular route. Moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 is not involved in metabolism. *In vitro* studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Herbal products, diet, smoking and alcohol use:

Because of topical route of administration and much lower systemic exposure compared to oral route, these extrinsic factors would not be expected to have implications on this ophthalmic product.

4.5 General Biopharmaceutics

4.5.1 Has the proposed commercial formulation been adequately linked to the Phase III clinical trial formulation?

Clinical pharmacology studies (Study C-01-16, C-01-48 and C-01-53) and the pivotal Phase 3 studies (Study C-01-46, C-01-55 and C-01-34) all used the commercial formulation of 0.5% moxifloxacin, although different batches were used. Because the proposed product is formulated as a solution, using different batches (same formulation) do not cause any significance in clinical outcomes.

4.6 Analytical

4.6.1 *What analytical method was used to determine moxifloxacin plasma concentrations? What are the lower and upper limits of quantification?*

Moxifloxacin concentrations were determined using a validated HPLC method and fluorescence detection. The method was developed and validated at Alcon. In this procedure, r. Following

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

Per the Alcon Technical Report 029:33:0702, stability of moxifloxacin in human plasma through at least

Long-term frozen storage stability assessment is in progress at the time of The time period between initiation of sample collection to last sample analyses was approximately , and stability data for more than are needed (see Comments to the sponsor). Because moxifloxacin in this application is not a new molecular entity, there are plasma assays for this compound in other NDA applications and the long-term stability requirement was fulfilled before. The sponsor will be asked to provide the updated long-term frozen stability information.

5 Labeling

Recommendations for changes to the proposed labeling are provided below (only affected sections are listed):

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9 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 ✓ § 552(b)(5) Draft Labeling

6.2 Individual Study Reviews

- 6.2.1** *Study C-01-16: A Fifteen-Day, Double-Masked, Randomized, Multiple-Dose Safety/Pharmacokinetic Study of Moxifloxacin Ophthalmic Solution Following Topical Ocular Administration in Normal, Healthy Male Japanese and Caucasian Subjects*

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A Fifteen-Day, Double-Masked, Randomized, Multiple-Dose Safety/Pharmacokinetic Study of Moxifloxacin Ophthalmic Solution Following Topical Ocular Administration in Normal, Healthy Male Japanese and Caucasian Subjects (C-01-16, Module 5, Volumes 6 & 7, 3.14-3.15)

Study Period: October 09, 2001 to November 21, 2001

Sample Analysis Period: June 13, 2002 to June 17, 2002

Investigator: _____

Study Center: _____

Objectives: To evaluate the safety and pharmacokinetics of Moxifloxacin HCl Ophthalmic Solution, 0.5%, following topical ocular administration in normal, healthy, male Japanese and Caucasian subjects.

Subjects: A total of 23 subjects (15 men and 8 women, age 20 to 64 were enrolled to receive drug or vehicle (Tables 1 and 2). In terms of race, 12 of them were Caucasians and 11 were Japanese. All were considered evaluable for the intent-to-treat and per protocol pharmacokinetic analysis.

Table 1. Baseline Demographic Characteristics

	Japanese Moxifloxacin		Japanese Vehicle		Caucasian Moxifloxacin		Caucasian Vehicle	
	N	%	N	%	N	%	N	%
Age								
20-64 years	7	100.0	4	100.0	8	100.0	4	100.0
Sex								
Male	7	100.0	4	100.0	8	100.0	4	100.0
Iris Color								
Brown	7	100.0	4	100.0	3	37.5	2	50.0
Hazel	0	0.0	0	0.0	0	0.0	1	25.0
Green	0	0.0	0	0.0	1	12.5	0	0.0
Blue	0	0.0	0	0.0	4	50.0	1	25.0

Table 2. Baseline Age and Physical Findings

		Mean	Std	Median	N	Min	Max
Japanese Moxifloxacin	Age (yr.)	45.1	7.5	45.0	7	32	54
	Height (in.)	66.2	2.8	67.0	7	62	69
	Weight (lb.)	153.0	20.6	158.0	7	114	176
Japanese Vehicle	Age (yr.)	45.8	3.8	44.5	4	43	51
	Height (in.)	63.5	3.8	65.0	4	58	66
	Weight (lb.)	191.5	44.0	174.0	4	162	256
Caucasian Moxifloxacin	Age (yr.)	41.9	12.0	41.5	8	26	60
	Height (in.)	70.8	1.8	70.5	8	68	73
	Weight (lb.)	179.0	20.2	173.0	8	155	215
Caucasian Vehicle	Age (yr.)	36.0	9.5	32.5	4	29	50
	Height (in.)	71.5	2.1	71.5	4	69	74
	Weight (lb.)	188.8	18.0	191.5	4	165	207

Study Design: The study was a single-center, randomized, double-masked, vehicle-controlled, parallel-group, multiple-dose safety/pharmacokinetic study in healthy male Japanese and Caucasian subjects. Subjects were randomized in a 2:1 (active:vehicle) ratio. The subjects will be applied either one drop of test drug solution or vehicle in each eye 3 times daily for 14 days (with the first dose dosed between 6:00 and 8:00 a.m., approximately 6 hour apart. A typical dosing time was 8:00 a.m., 2:00 p.m. and 8:00 p.m.), with an additional dose on the morning of Day 15. In Japan, 14 days of TID dosing represents the maximum intended duration for the treatment of extraocular bacterial infections (e.g., conjunctivitis). Subjects were fasted overnight for 10 hours after the Day 14 visit (*Reviewer's comment: it is not clear why this procedure is necessary*). The moxifloxacin vehicle group was included to maintain masking and to enable an untreated comparison for safety summaries.

Following an initial Screening visit, subjects that qualified were screened for check-in. At the Day 1 visit, subjects were randomized according to race in a 2:1 ratio to vehicle (i.e., seven male Japanese and eight male Caucasian subjects assigned to Moxifloxacin 0.5% and four male Japanese and four male Caucasian subjects assigned to Moxifloxacin Vehicle).

Dosage and Administration: Moxifloxacin Ophthalmic Solution, 0.5%, Batch number 00-500222-1, Formulation identification number 101149, in 5.0 mL Opaque DROP-TRAINER (ODT) bottles, one drop in each eye 3 times daily on Day 1 through Day 14 with one final dose the morning of Day 15.

Each mL of Moxifloxacin solution ————— contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base (see Table 3 below)

Table 3. Components of 0.5% Moxifloxacin Solution

Component	% w/v	Function
Moxifloxacin HCl	0.545	Active Ingredient
Sodium Chloride	—	—
Boric Acid	—	—
Sodium Hydroxide Hydrochloric Acid	pH Adjustments (final pH 6.8)	pH Adjusters
Purified Water	—	—

Reference Therapy, Dose and Mode of Administration: Moxifloxacin vehicle, Lot 00-500202-1, Formulation identification number 101611, in 5.0 mL Opaque DROP-TRAINER (ODT) bottles, one drop in each eye three times daily (TID) on Day 1 through Day 14 with one final dose the morning of Day 15.

Sample Collection and Handling:

Days 4, 7, and 11: 0 min (Trough sample prior to morning dose)
Day 14: 0 min (pre-dose), Post dose at the following times: 0.25, 0.5, and 1 hour
Approximately seven mL of blood samples were collected using EDTA as anticoagulant for plasma moxifloxacin determination. Samples were stored at -70°C prior to shipping. Sample collection and storage condition were consistent with requirements as determined during method validation.

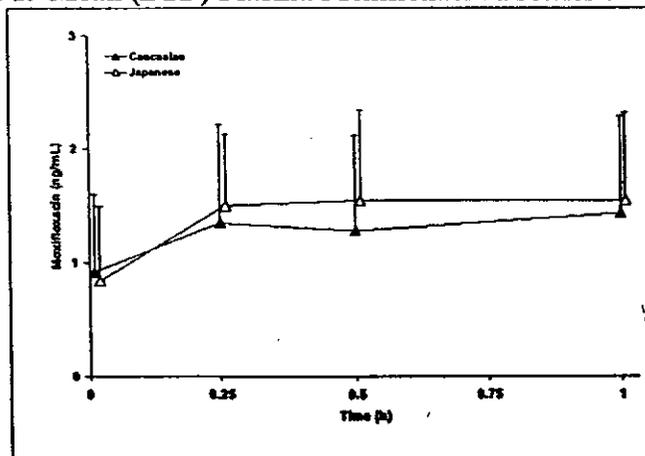
Sample Analysis: In accordance with the protocol, plasma samples from the vehicle group were not assayed for bioanalysis, thus bioanalytical results from 15 subjects who received Moxifloxacin 0.5% were available for pharmacokinetic analyses. Moxifloxacin concentrations were determined using a validated HPLC method with _____ and fluorescence detection. Moxifloxacin concentrations were determined using a validated HPLC method _____) and fluorescence detection. The working range of the procedure was _____. The details were described in Section 4.6 (OCPB review) and reported in Alcon Technical Report No. 026:33:0602, Page 461 (Module 5, Vol. 7).

Pharmacokinetic and Statistical Analysis: The primary pharmacokinetic evaluations included: plasma concentrations at each sampling time, pre-dose plasma levels on Days 4, 7, 11 and 14 (C_{min}), peak plasma concentration (C_{max}) on Day 14, and time to reach peak concentration (T_{max}) on Day 14. Descriptive statistics were calculated for the plasma concentrations at each sampling time and the pharmacokinetic assessment of C_{min} , C_{max} , and T_{max} . For the calculation of mean plasma concentration at each time point and mean pharmacokinetic parameters (C_{min} and C_{max}), drug concentrations that were below the level of quantitation (LOQ) were replaced with one-half the limit of quantitation (_____) ng/mL (Reviewer's comments: *The agency does not agree with this approach. The BLQ values should be replaced with "0". Both mean of all values and mean of measurable values need to be calculated*). Pharmacokinetic plasma analyses were not performed for subjects dosed with moxifloxacin vehicle.

The pre-dose sampling on Days 4, 7, 11 and 14 were chosen to assess the time required to achieve steady-state conditions.

Pharmacokinetic Results: Based on the drug concentration (0.5%), a 38 μ L drop size and a regimen of 1 drop in each eye, each single dose of moxifloxacin was 380 μ g. The daily dose was 1140 μ g. As pre-specified in the protocol, the samples from the Vehicle group were not assayed for bioanalysis. The mean Day 14 plasma concentration versus time profile for moxifloxacin is presented in Figure 1. Quantifiable plasma moxifloxacin concentrations were seen in 7 of 7 Japanese and 6 of 8 Caucasian subjects on Day 14. Limited quantifiable () predose plasma moxifloxacin concentrations were available from Japanese and Caucasian subjects on Day 4, Day 7, Day 11 and Day 14. These concentrations were very low and ranged from BLQ to () in Caucasian subjects and from BLQ to () in Japanese subjects (Table 4). Comparison of pre-dose plasma concentrations on Days 4, 7, 11, and 14 indicated that all subjects had attained steady-state after 3 days of dosing (Table 4). On Day 14, peak steady-state plasma concentrations (C_{max}) observed between 0.25 and 1.0 hours post dose ranged from below the level of quantification (BLQ, ()) (mean 1.41 ± 1.05 ng/mL) in 8 Caucasian subjects (*Reviewer's note: The mean value was calculated by the reviewer replacing BLQ values with "0". The mean and standard deviation for all measurable value was 1.88 ± 0.69 ng/mL.*) and from () (mean 1.67 ± 0.79 ng/mL) in 7 Japanese subjects (Table 4). The steady-state plasma moxifloxacin C_{min} , C_{max} and T_{max} values following 14 1/3 days of TID dosing were similar in magnitude in both Japanese and Caucasian subjects. However, the values (both predose and C_{max} values) were lower than those obtained in Study C-01-48 (Table 5) for both races (almost 50% lower). Sampling in this study was limited (only three timepoints up to 1 hr). For some subjects, C_{max} may reach at a later timepoint (samples were not collected) which might explain the lower C_{max} values in this study. Because levels of moxifloxacin were low and variable, it was likely that the differences were also due to noises.

Figure 1. Mean (\pm SD) Plasma Moxifloxacin Profiles on Day 14



Mean (\pm SD) plasma moxifloxacin profiles on Day 14 are presented. Plasma samples were collected at 0.25, 0.5 and 1 hour after the 8 AM dose. Data points are staggered for the purpose of graphical presentation (Intent-to-Treat PK Data).

Table 4. Mean (\pm SD) Plasma Moxifloxacin Profiles

(Reviewer's note: Please ignore the mean and SD values of C_{min} and Caucasian C_{max} in the table that need to be recalculated by replacing BLQ values with "0". The recalculated value of C_{max} for Caucasian is 1.41 ± 1.05 ng/mL.)

Ethnicity	Subject #	Plasma C_{min} ^a (ng/mL)				C_{max} ^a (ng/mL)	T_{max} (h)
		Day 4	Day 7	Day 11	Day 14	Day 14	
Caucasian	102						
	103						
	104						
	105						
	107						
	108						
	111						
	112						
	Mean	0.80	BLQ ^b	0.90	0.92	1.51	0.59
	SD	0.66	NA	0.58	0.68	0.91	0.35
	N	8	8	8	8	8	8
	Min						
	Max						
Japanese	201						
	203						
	204						
	205						
	207						
	208						
	210						
		Mean	BLQ ^b	BLQ ^b	BLQ ^b	0.84	1.67
	SD	NA	NA	NA	0.66	0.79	0.34
	N	7	7	7	7	7	7
	Min						
	Max						

^a Below the limit of quantification (BLQ) values were replaced with $\frac{1}{2}$ the limit of quantification (LOQ) for calculating the mean values. LOQ/ — NA=Not applicable

^b Mean < BLQ is defined as BLQ

Table 5. Comparison of Moxifloxacin Exposure between Study C-01-16 and Study C-01-48.

	Japanese		Caucasian	
	C-01-16	C-01-48	C-01-16	C-01-48
C_{min} on Day 4 (ng/mL)	Mean < BLQ (0.75 ng)	$1.40 \pm 0.57^*$	0.57 ± 0.86	$1.12 \pm 0.54^*$
C_{max} at Steady State (ng/mL)	1.67 ± 0.79 (Day 14)	3.04 ± 1.37 (Day 5)	1.41 ± 1.05 (Day 14)	2.50 ± 1.24 (Day 5)

*Reviewer's note: Data for reference only. The mean and SD values of C_{min} in the study C-01-048 need to be recalculated by replacing BLQ values with "0". However, because only a few subjects with BLQ values, the corrected number will not be very different.

Conclusion: The pharmacokinetic results following TID topical ocular dosing of Moxifloxacin 0.5% in this study confirmed very low systemic exposure to moxifloxacin in both Japanese and Caucasian subjects. Mean peak plasma concentrations (Day 14) were approximately 1.6 ng/mL and were observed within 1.0 hour of dosing. The steady-state peak plasma concentrations observed in this study were in the same ballpark of those observed in a similar Alcon study, Study C-01-48. Overall, the maximum individual plasma concentrations found in the present study ([redacted] in Caucasian and Japanese subjects, respectively) are about 1000-fold lower than the mean C_{max} (3.24 μ g/mL) in volunteers who were administered the currently marketed 400 mg oral dose of Moxifloxacin HCl. The steady-state pharmacokinetic parameters of moxifloxacin (C_{min} , C_{max} and T_{max}) are similar in Japanese and Caucasian subjects.

**APPEARS THIS WAY
ON ORIGINAL**

6.2.2 *Study C-01-48: An Open-Label, Single Center, Multiple-Dose Pharmacokinetic Study of Moxifloxacin Ophthalmic Solution 0.5% Following Topical Ocular Administration in Healthy Male and Female Adult Volunteers*

**APPEARS THIS WAY
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**APPEARS THIS WAY
ON ORIGINAL**

An Open-Label, Single Center, Multiple-Dose Pharmacokinetic Study of Moxifloxacin Ophthalmic Solution 0.5% Following Topical Ocular Administration in Healthy Male and Female Adult Volunteers (C-01-48, Module 5, Volumes 2 & 3, 3.10-3.11)

Study Period: November 01, 2001 to December 21, 2001

Sample Analysis Period: May 12, 2002 to June 28, 2002

Investigators: —

Study Center: —
—

Objectives: To evaluate the safety and pharmacokinetics of Moxifloxacin HCl Ophthalmic Solution, 0.5%, in healthy adult male and female volunteers following topical ophthalmic dosing, administered 3 times daily for 4 days with a final dose on the morning of Day 5.

Subjects: A total of 21 subjects (9 men and 12 women, age 18 to 55 (36 ± 11.5 , mean \pm SD)) were enrolled to receive drug (Tables 1 and 2). In terms of race, 13 of them were Caucasian and 8 were Japanese. All were considered evaluable for pharmacokinetic analysis. No subject was excluded because of protocol violations. Therefore, the per-protocol and intent-to-treat data sets were identical.

All Asian subjects in this study were documented by the clinical testing facility as 1st, 2nd or 3rd generation Japanese, based on interviews with the subjects during the screening visit (all 4 grandparents of each Japanese subject enrolled in the study were born in Japan). The diet the Japanese subjects consumed while in house was consistent with meals consumed in Japan. This diet plan was used to ensure that the Japanese study participants were as representative of the population of Japan as possible, thereby eliminating any effect diet may play on pharmacokinetic data results. Any references to Asian subjects in this clinical study report may be considered as references to Japanese subjects.

Table 1. Baseline Demographic Characteristics

	N	%
Age		
18-55	21	100
Race		
Caucasian	13	61.9
Asian (Japanese)	8	38.1
Sex		
Male	9	42.9
Female	12	57.1

Table 2. Summary Statistics For Age, Height, and Weight (All Subjects, N=21)

	Mean	Std	Min	Max
Age (y)	36	11.5	18	55
Height (in)	67	4.2	59	73
Weight (lb)	145	20.9	110	179

Study Design: The study was an open-label, single-center, multiple-dose pharmacokinetic study in healthy male and female volunteers. The subjects were applied one drop of test drug solution in each eye 3 times daily (every 8 hours with the first dose dosed between 6:00 and 8:00 a.m.) for four days, with an additional dose on the morning of Day 5.

Dosage and Administration: Moxifloxacin Ophthalmic Solution, 0.5%, Batch number 00-500212-1, in 5.0 mL Opaque DROP-TRAINER bottles, one drop in each eye 3 times daily for four days, with an additional dose on the morning of Day 5

Each mL of Moxifloxacin solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base (see Table 3 below)

Table 3. Components of 0.5% Moxifloxacin Solution

Component	% w/v	Function
Moxifloxacin HCl	0.545	Active Ingredient
Sodium Chloride	—	—
Boric Acid	—	—
Sodium Hydroxide Hydrochloric Acid	pH Adjustments (final pH 6.8)	pH Adjusters
Purified Water	—	—

Sample Collection and Handling:

Day 1: 0 min (pre-dose prior to morning dose), Post morning dose at the following times: 15 min, 30 min, 1, 2, 4, 6, and 8 hrs (the 8-hour sample was drawn before the second 8-hour dose)

Day 2: 0 min (Trough sample prior to morning dose)

Day 3: 0 min (Trough sample prior to morning dose)

Day 4: 0 min (Trough sample prior to morning dose)

Day 5: 0 min (pre-dose), Post dose at the following times: 15 min, 30 min, 1, 2, 4, 6, 8, 12, 24 (Day 6), 36 (Day 6) and 48 (Day 7) hrs

10 mL blood samples were collected using EDTA as anticoagulant for plasma moxifloxacin determination. Samples were stored at -70°C prior to shipping. Sample collection and storage condition were consistent with requirements as determined during method validation. (Reviewer's note: The long-term frozen stability assessment of moxifloxacin in human plasma was in progress at the time of submission. The agency will ask the sponsor to submit updated stability information).

Sample Analysis: Moxifloxacin concentrations were determined using a validated HPLC method. The working range of the procedure was —. The details were described in Section 4.6 (OCPB

review) and reported in Alcon Technical Report No. 025:33:0602, page 500 (Module 5, Vol. 2).

Pharmacokinetic and Statistical Analysis: The following pharmacokinetic parameters were estimated using model independent methods: the observed pre-dose drug concentrations (C_{min}) on Days 2, 3, 4, and 5; the observed maximum drug concentration (C_{max}) on Day 1 and Day 5; the time of the maximum drug concentration (T_{max}) on Days 1 and 5; the area under the drug concentration time curve over the 8-hr dosing interval on Day 1 and Day 5 (AUC_{0-8}); the elimination half-life ($T_{1/2}$) as well as the area under the drug concentration time curve from zero to infinity ($AUC_{0-\infty}$). Descriptive statistics were provided for all subjects, and separately for gender and race. Drug concentrations that were below the level of quantitation (LOQ) were replaced with $\frac{LOQ}{2}$ the limit of quantitation (e.g., $\frac{LOQ}{2}$), for the calculation of mean plasma concentrations. (Reviewer's comments: The agency does not agree with this approach. The BLQ values should be replaced with "0". Both mean of all values and mean of measurable values need to be calculated). For subjects with insufficient data for pharmacokinetic evaluation, only C_{max} values were reported. The data did not support the calculation of AUC_{0-48} as specified in protocol.

C_{max} and AUC were used to evaluate the systemic exposure of drugs. The pre-dose plasma concentration measurements taken on Day 2 through Day 5 were used to establish the steady-state conditions. The C_{max} and AUC_{0-8} values obtained after the first-dose and last-dose were used to determine the plasma accumulation of moxifloxacin, if any, following a multiple dosing regimen. The predicted accumulation ratio, based on the elimination rate constant (λ_z), was calculated using the formula:

$$R_{ac} = 1/(1 - e^{(-\lambda_z \tau)})$$

where " τ " is the dosing interval.

Pharmacokinetic Results: Based on the drug concentration (0.5%), a 38 μ L drop size and a regimen of 1 drop in each eye, each dose of moxifloxacin was 380 μ g. The daily dose was 1140 μ g.

Single Dose Pharmacokinetics

After the first dose, plasma samples with quantifiable moxifloxacin concentrations (≥ 0.75 ng/mL) were obtained in 16 of 21 subjects. Figure 1 represents the mean \pm SD plasma concentration time profile of moxifloxacin following the first topical dose. The individual and mean pharmacokinetic parameters are shown in Table 4. All intended pharmacokinetic parameters could not be estimated from all subjects because plasma samples with quantifiable moxifloxacin concentrations (≥ 0.75 ng/mL) were limited. After the first dose, mean C_{max} was 1.22 ± 0.83 ng/mL ($\frac{LOQ}{2}$). (Reviewer's note: The mean value was calculated by the reviewer replacing BLQ values with "0". The mean and standard deviation for all measurable value was 1.60 ± 0.53 ng/mL.) Peak concentrations were observed within 0.25 to 2.0 hrs (mean 0.5 hr) (Table 4). Thereafter, plasma concentrations declined in a biphasic manner, with an apparent elimination half-life of about 8.4 hours. Systemic exposure was also estimated from the area under the concentration-time curve (AUC) for the 10 of 21 subjects that had sufficient plasma

concentration data. The AUC for moxifloxacin over the 8 hr sampling period (AUC_{0-8}) ranged from 4.0 $ng \cdot h/mL$ to 10.4 $ng \cdot h/mL$ (mean 7.3 ± 2.3 $ng \cdot h/mL$). After a single dose (1 drop per eye) of 0.5% moxifloxacin solution, the C_{max} and $AUC_{0-\infty}$ values (systemic exposure) were approximately 2000–times lower than those from a single therapeutic dose of IV (400 mg) or oral (400 mg) moxifloxacin (Table 5). The bioavailability was approximately 35% via topical ocular route.

Figure 1. Mean \pm SD Moxifloxacin Plasma Profile Following the First Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Subjects

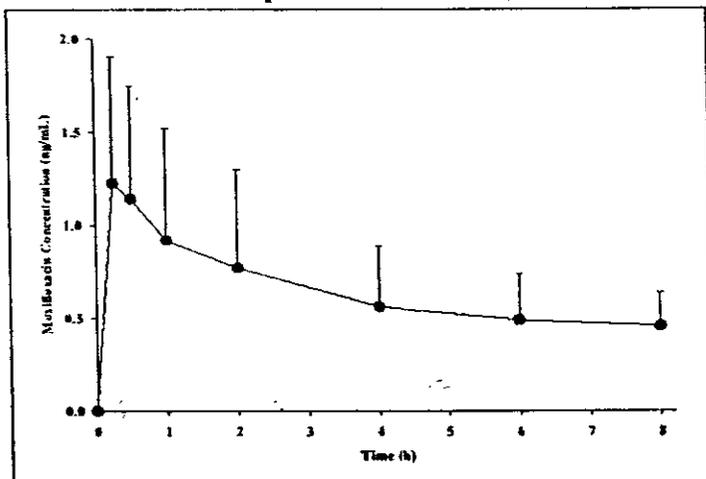


Table 4. Pharmacokinetic Parameters for Moxifloxacin on Day 1 Following the First Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Subjects
(Reviewer's note: Please ignore the mean and SD values of C_{max} in the table that were recalculated by replacing BLQ values with "0". The recalculated value is 1.22 ± 0.83 ng/mL .)

Subject No.	Gender	Race	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-8} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
101	Male	Asian	(BLQ)*	NC	NC	NC	NC
102	Male	Caucasian	1.29	0.25	NC	NC	NC
103	Female	Caucasian	1.04	0.50	3.3	11.0	NC
104	Female	Caucasian	1.64	0.50	8.6	23.6	13.3
105	Male	Asian	2.21	0.52	6.1	6.2	NC
106	Female	Caucasian	2.29	0.48	10.4	18.0	6.6
107	Female	Caucasian	2.12	2.00	NC	NC	NC
108	Female	Asian	2.17	0.25	9.9	25.4	18.9
109	Female	Asian	0.80	0.50	NC	NC	NC
110	Female	Caucasian	2.24	0.25	7.3	19.2	4.7
111	Female	Caucasian	1.84	0.25	4.4	4.4	NC
112	Female	Asian	1.30	0.25	4.6	4.1	NC
113	Male	Caucasian	(BLQ)*	NC	NC	NC	NC
114	Male	Caucasian	1.93	0.25	7.8	12.7	7.4
115	Female	Asian	1.48	0.88	9.3	18.0	7.4
116	Female	Asian	1.05	0.25	NC	NC	NC
117	Male	Caucasian	(BLQ)*	NC	NC	NC	NC
118	Female	Caucasian	(BLQ)*	NC	NC	NC	NC
119	Male	Asian	0.88	0.50	NC	NC	NC
120	Male	Caucasian	(BLQ)*	NC	NC	NC	NC
121	Male	Caucasian	1.14	0.25	NC	NC	NC
		Mean	1.31	0.49	7.3	13.2	8.4
		SD	0.78	0.44	2.3	7.3	3.1
		N	21	12	10	10	6
		N/N	(BLQ)*				
		Mean					

* Samples were below the limit of quantitation (BLQ); BLQ values were replaced by 0 for the calculation of the mean C_{max} .

NC- Not calculated because of insufficient data

Table 5. Comparison of Moxifloxacin Exposure after a Single Dose of Ophthalmic Solution (0.5%), IV Infusion and Oral Tablet.

	Ophthalmic Solution (0.5%)	IV	Multiple (6x1/Ophthalmic)	Oral	Multiple (6x1/Ophthalmic)
Dose	1 drop per eye (~0.38 mg)	400 mg (1 hr Infusion)	400 mg (1 hr Infusion)	400 mg	400 mg
C _{max}	1.6 ± 0.5 ng/mL	3.9 ± 0.9 µg/mL	3.9 ± 0.9 µg/mL	3.1 ± 1.0 µg/mL	3.1 ± 1.0 µg/mL
AUC _{0-∞}	13.2 ± 7.3 ng•h/mL	39.3 ± 8.6 µg•h/mL	39.3 ± 8.6 µg•h/mL	36.1 ± 9.1 µg•h/mL	36.1 ± 9.1 µg•h/mL

Data for IV and oral moxifloxacin are from Avelox package inserts.

Steady State Assessment

Comparison of pre-dose plasma moxifloxacin concentrations on Day 2, Day 3, Day 4, and Day 5 (Table 6), using repeated measures analysis of variance, indicated no difference between Days 3, 4, and 5; and that all subjects had attained steady-state by Day 3 (Table 7).

Table 6. Predose Concentrations of Moxifloxacin on Days 2, 3, 4, and 5.

Visit	Mean ± SD (N=21) ^a	Mean ± SD (N=21) ^b	Mean ± SD ^c	Min	Max
Day 2	0.91 ± 0.50	0.76 ± 0.66	1.23 ± 0.33 (N=13)	BLQ	—
Day 3	1.27 ± 0.60	1.20 ± 0.72	1.48 ± 0.44 (N=17)	BLQ	—
Day 4	1.23 ± 0.56	1.17 ± 0.65	1.37 ± 0.46 (N=18)	BLQ	—
Day 5	1.25 ± 0.58	1.18 ± 0.70	1.46 ± 0.43 (N=17)	BLQ	—

^a Below the LOQ values were replaced with — (the LOQ) for calculating the mean values (Sponsor's analysis).

^b Below the LOQ values were replaced with "0" for calculating the mean values (Reviewer's analysis).

^c Mean and standard deviation for measurable values (Reviewer's analysis).

Table 7. Assessment of Steady-State Based on Pre-Dose Moxifloxacin Concentrations in Healthy Subjects

Visit 1	Visit 2	t-value	Pr > t ^a
Day 2	Day 3	-5.05	<0.0001
	Day 4	-4.39	<0.0001
	Day 5	-4.80	<0.0001
Day 3	Day 4	0.65	0.5164
	Day 5	0.25	0.8042
Day 4	Day 5	-0.40	0.6884

^a Based on repeated measures of analysis. See Section 6.0 of the Biostatistics Report for details (page 335).

Multiple Dose Pharmacokinetics

After the last topical ocular dose on the morning of Day 5, quantifiable plasma concentrations of moxifloxacin were seen in all 21 subjects. The mean plasma concentration-time profile is shown in Figure 2. The individual and mean pharmacokinetic parameters following the last topical dose on the morning of Day 5 are listed in Table 8. After the last topical dose, steady-state peak plasma concentrations (C_{max}) of moxifloxacin ranged from _____ mean 2.70 ± 1.29 ng/mL) and were observed from 0.23 to 2.0 hr post-dose (mean 0.57 hr). Systemic exposure was further estimated by determining the area under the concentration-time curve for the 19 of 21 subjects with sufficient plasma data following the last topical dose. The steady-state mean AUC_{0-8} value on Day 5 was 15.0 ± 5.3 ng•h/mL (range _____). For those subjects with sufficient data for analysis, moxifloxacin half-life estimates ranged from 7 h to 19.7 h (mean 13.1 ± 3.3 h), similar to what was reported in healthy subjects after IV and oral dosing (12-15 hr). The dose (approximately 380 μ g) on Day 5 in this study was ~1050-times lower than the therapeutic oral 400 mg tablet (AVELOX®) moxifloxacin studied by Bayer for NDA 21-085. The mean steady state peak concentration obtained was approximately 1600-times lower than those reported after a therapeutic 400 mg oral and IV dose (4.2-4.5 μ g/mL) (Table 9). After multiple dose (1 drop per eye TID for four days) of 0.5% moxifloxacin solution, the steady-state C_{max} and estimated daily AUC values (systemic exposure) were approximately 1500-times and 1000-times lower than those from multiple therapeutic dose of IV (400 mg) or oral (400 mg) moxifloxacin (Table 9).

Figure 2. Mean \pm SD Moxifloxacin Plasma Profile Following the Last Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Subjects

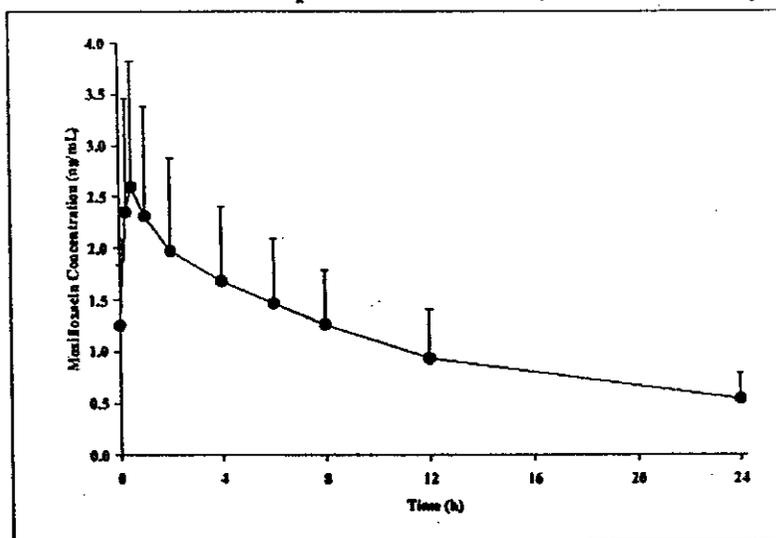


Table 8. Pharmacokinetic Parameters for Moxifloxacin on Day 5 Following the Last Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Subjects

Subject	Gender	Race	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₈ (ng·h/mL)	AUC ₀₋₂₄ (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	t _{1/2} (h)
101	Male	Asian						
102	Male	Caucasian						
103	Female	Caucasian						
104	Female	Caucasian						
105	Male	Asian						
106	Female	Caucasian						
107	Female	Caucasian						
108	Female	Asian						
109	Female	Asian						
110	Female	Caucasian						
111	Female	Caucasian						
112	Female	Asian						
113	Male	Caucasian						
114	Male	Caucasian						
115	Female	Asian						
116	Female	Asian						
117	Male	Caucasian						
118	Female	Caucasian						
119	Male	Asian						
120	Male	Caucasian						
121	Male	Caucasian						
		Mean	2.70	0.57	15.0	30.2	41.9	13.1
		SD	1.29	0.40	5.3	9.8	15.6	3.3
		N	21	21	19	19	19	19
		Min						
		Max						

NC - Not calculated because of insufficient data.

Table 9. Comparison of Moxifloxacin Exposure after Multiple Daily Dose of Ophthalmic Solution (0.5%), IV Infusion and Oral Tablet.

	Ophthalmic Solution (0.5%)	IV	Multiples (IV/Ophthalmic)	Oral	Multiples (Oral/Ophthalmic)
Daily Dose	1 drop per eye TID (~1.14 mg)	400 mg (1 hr Infusion)	351	400 mg	351
C _{max} at Steady State	2.7 ± 1.3 ng/mL	4.2 ± 0.8 µg/mL	1556	4.5 ± 0.5 µg/mL	1667
Daily AUC ₀₋₂₄ at Steady State	45 ng·h/mL*	38.0 ± 4.7 µg·h/mL	844	48.0 ± 2.7 µg·h/mL	1067

Data for IV and oral moxifloxacin are from Avelox package inserts.

Estimated: AUC₀₋₂₄, TID on Day 5 = 3 AUC₀₋₈, single dose on Day 5 = 3*15 ng·h/mL = 45 ng·h/mL.

Comparison of Day 1 and Day 5 Pharmacokinetic Parameters

The mean and range of steady-state peak plasma concentrations of moxifloxacin were generally higher on Day 5 compared to Day 1 (Figure 3 and Table 10). Accumulation ratios of moxifloxacin in plasma were estimated 3 ways: 1) observed individual C_{max} on Day 5/ C_{max} on Day 1; 2) estimated individual AUC₀₋₈ on Day 5/ AUC₀₋₈ on Day 1;

and 3) based on terminal phase elimination rate constant (λ_z) and three times-a-day dosing. By these methods, the mean accumulation ratios were approximately 2.0, 2.5, and 2.9, respectively (Table 11). The accumulation ratios by all 3 methods were comparable.

Figure 3. Mean \pm SD Moxifloxacin Plasma Profile Following the First and Last Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Subjects

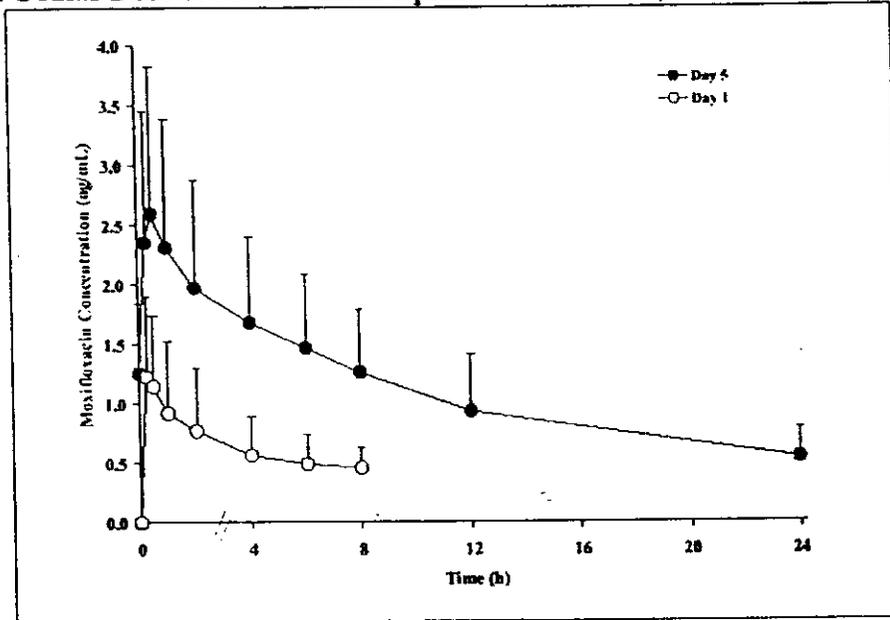


Table 10. Mean \pm SD (Range) Plasma Pharmacokinetic Parameters on Day 1 and Day 5 Following the Topical Ocular Administration of Moxifloxacin Ophthalmic Solution, 0.5%, in Healthy Volunteers

(Reviewer's note: Please ignore the mean and SD values of C_{max} in the table that were recalculated by replacing BLQ values with "0". The recalculated value is 1.22 ± 0.83 ng/mL.)

Parameter	Day 1	Day 5
C_{max} (ng/mL)	1.31 ± 0.70^a	2.70 ± 1.29^a
T_{max} (h)	0.49 ± 0.44^b	0.57 ± 0.40^b
AUC_{0-8} (ng-h/mL)	7.3 ± 2.3^d	--
$AUC_{0-8, steady state}$ (ng-h/mL)	--	15.0 ± 5.3^c
$AUC_{(0-\infty)}$ (ng-h/mL)	13.2 ± 7.3^d	41.9 ± 15.6
$t_{1/2}$ (h)	8.4 ± 3.1^e	13.1 ± 3.3^e

^aN = 21 ; samples below the limit of quantitation (BLQ) were replaced by one-half the limit of quantitation for the calculation of mean C_{max} .

^bN = 16

^cN = 19

^dN = 10

^eN = 6

C_{max} = Maximum plasma concentration observed.

T_{max} = Time after dosing at which C_{max} was observed.

Table 11. Accumulation Ratios Based on Observed C_{max} and AUC_{0-8} Compared to Those Predicted Based on Terminal Phase Elimination Rate (λ_z) Following the Last Dose.

Subject No.	Gender	Race	Ratio Day 5/Day 1		Accumulation Ratio (R_{ac}) ^c
			C_{max} ^a	AUC ^b	
101	Male	Asian			
102	Male	Caucasian			
103	Female	Caucasian			
104	Female	Caucasian			
105	Male	Asian			
106	Female	Caucasian			
107	Female	Caucasian			
108	Female	Asian			
109	Female	Asian			
110	Female	Caucasian			
111	Female	Caucasian			
112	Female	Asian			
113	Male	Caucasian			
114	Male	Caucasian			
115	Female	Asian			
116	Female	Asian			
117	Male	Caucasian			
118	Female	Caucasian			
119	Male	Asian			
120	Male	Caucasian			
121	Male	Caucasian			
	Mean		2.0	2.5	2.9
	SD		1.1	0.8	0.6
	N		16	10	19
	Min				
	Max				

^a $R_{ac} = C_{max (Day 5)} / C_{max (Day 1)}$

^b $R_{ac} = AUC_{0-8 (Day 5)} / AUC_{0-8 (Day 1)}$

^c $R_{ac} = 1 / (1 - e^{-\lambda_z \cdot t})$

NC= Not calculated due to lack of quantifiable plasma data either on Day 1 or Day 5.

Subgroup Analysis of Pharmacokinetic Parameters

Effect of Gender

The mean plasma concentration-time profiles following the last topical dose for moxifloxacin in male and female subjects without regard to race are presented in Figure 4a and Figure 4b. Mean plasma moxifloxacin concentrations were higher in females than in males. After the last topical dose in the morning of Day 5 the mean peak plasma concentrations of moxifloxacin in females was 3.18 ± 1.34 ng/mL (range —) compared to 2.08 ± 0.94 ng/mL (range —) in males. The mean peak plasma concentrations, standard deviations, and ranges for the moxifloxacin pharmacokinetic parameters are presented in Table 12. In females, the mean C_{max} , AUC_{0-8} , and $AUC_{0-\infty}$ values were 52%, 22%, and 35% higher, respectively, than in males. When normalized to body weight differences, the difference in C_{max} , and AUC values were decreased (30%, 5%, and 16% higher, respectively). The higher C_{max} and AUC in females as compared to males appear to be related to body weight differences in females compared to males, and might not be due to any gender related differences in metabolism or elimination of moxifloxacin. According to the Avelox oral tablet labeling,

the mean AUC and C_{max} were 8% and 16% higher in females compared to males after 400 mg daily dosing for 10 days in healthy subjects. There are no significant differences between male and female subjects when differences in body weight are taken into consideration. In the current study, because levels were low and variable, it was likely that the differences were also due to noises. Gender difference in terms of moxifloxacin exposure due to route of administration would not be anticipated. The effect of gender could not be evaluated separately in Asian and Caucasian subjects because an insufficient number of male and female subjects were available.

Figure 4a. Mean \pm SD Moxifloxacin Plasma Profiles Following the Last Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Male and Female Subjects. (Non-normalized data; sample times are staggered for presentation purposes.)

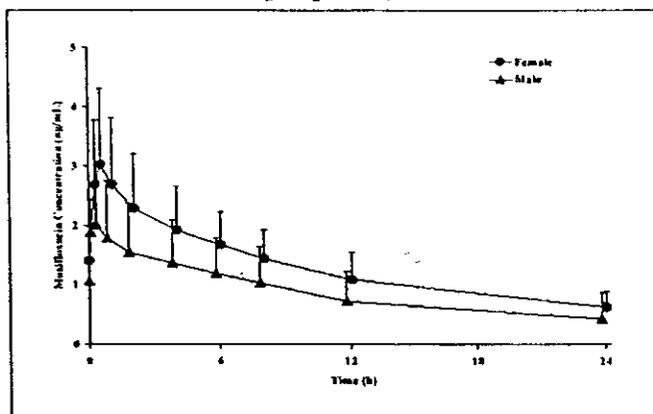


Figure 4b. Mean \pm SD Moxifloxacin Plasma Profiles Following the Last Topical Ocular Dose of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Male and Female Subjects (Data normalized to 70 kg body weight; sample times are staggered for presentation purposes.)

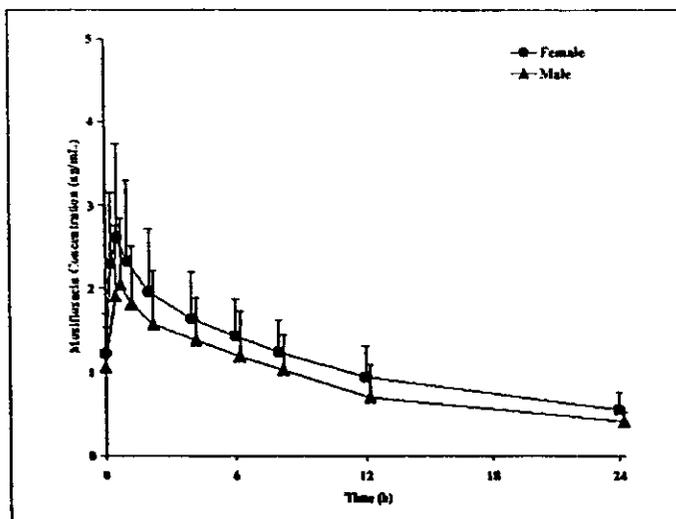


Table 12. Mean ± SD (Range) Moxifloxacin Plasma Pharmacokinetic Parameters by Gender on Day 5, following the Last Topical Ocular Administration of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Volunteers

Parameter	Male (N=9)	Female (N=12)	Pooled (N=21)
C_{max} (ng/mL)	2.08 ± 0.94	3.18 ± 1.34	2.70 ± 1.29
$C_{max, norm}^a$ (ng/mL)	2.10 ± 0.77	2.74 ± 1.19	2.47 ± 1.06
T_{max} (h)	0.44 ± 0.24	0.67 ± 0.48	0.57 ± 0.40
AUC_{0-8} (ng·h/mL)	13.1 ± 4.2	16.1 ± 5.7	15.0 ± 5.3
$AUC_{0-8, norm}^b$ (ng·h/mL)	13.2 ± 2.7	13.8 ± 4.6	13.6 ± 3.9
$AUC_{0-∞}$ (ng·h/mL)	34.2 ± 10.4	46.3 ± 16.7	41.9 ± 15.6
$AUC_{0-∞, norm}^c$ (ng·h/mL)	34.4 ± 6.3	39.8 ± 13.6	37.8 ± 11.5
$t_{1/2}$ (h)	11.3 ± 1.9	14.1 ± 3.5	13.1 ± 3.3

^a $C_{max, norm}$ = Maximum observed plasma concentration, normalized to 70 kg body weight.

^b $AUC_{0-8, norm}$ = Area under the concentration-time curve from time zero to 8 hours, normalized to 70 kg body weight.

^c $AUC_{0-∞, norm}$ = Area under the concentration-time curve from time zero to infinity, normalized to 70 kg body weight.

Effect of Race

The enrollment of 8 Asian and 13 Caucasian subjects made possible the evaluation of the effect of race on the pharmacokinetics of moxifloxacin. After the last topical dose on the morning of Day 5, steady-state plasma concentrations of moxifloxacin were available from all 21 subjects. The mean steady-state plasma concentration-time profiles for moxifloxacin by race without regard to gender are presented in Figure 5. Over the 24-hour sampling period, plasma moxifloxacin concentrations were comparable in both Asian and Caucasian subjects. The mean steady-state peak plasma concentration of moxifloxacin in Asian subjects was 3.04 ± 1.37 ng/mL (range _____) which was slight higher than the mean of 2.50 ± 1.24 ng/mL (range _____) observed in Caucasian subjects (22% higher) (Table 13). The difference reduced slightly (to 18%) after normalized by body weight. The differences in AUC values are small between races. Because levels were low and variable in this study, it was likely that the differences were also due to noises. According to the Avelox oral tablet labeling, steady-state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those determined in Caucasians. Racial difference in terms of moxifloxacin exposure due to route of administration would not be anticipated.

Figure 5. Mean \pm SD Moxifloxacin Plasma Pharmacokinetic Parameters in Healthy Asian and Caucasian Volunteers on Day 5 Following the Last Topical Ocular Administration of Moxifloxacin Ophthalmic Solution, 0.5%. (Sample times are staggered for presentation purposes.)

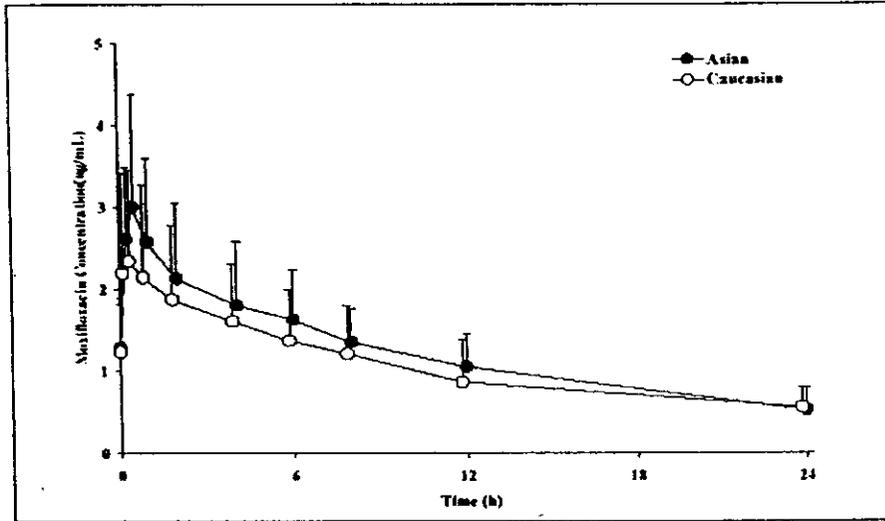


Table 13. Mean \pm SD (Range) Plasma Pharmacokinetic Parameters on Day 5 Following the Last Topical Ocular Administration of Moxifloxacin Ophthalmic Solution, 0.5% in Healthy Asian and Caucasian Volunteers

Parameter	Caucasian (N = 13)	Asian (N = 8)	Pooled (N = 21)
C_{max} (ng/mL)	2.50 \pm 1.24	3.04 \pm 1.37	2.70 \pm 1.29
$C_{max, norm}^a$ (ng/mL)	2.31 \pm 0.95	2.73 \pm 1.23	2.47 \pm 1.06
T_{max} (h)	0.48 \pm 0.26	0.72 \pm 0.56	0.57 \pm 0.40
AUC_{0-8} (ng-h/mL)	14.8 \pm 5.1	15.3 \pm 5.9	15.0 \pm 5.3
$AUC_{0-8, norm}^b$ (ng-h/mL)	13.5 \pm 3.7	13.6 \pm 4.5	13.6 \pm 3.9
$AUC_{0-\infty}$ (ng-h/mL)	41.0 \pm 16.1	43.1 \pm 15.9	41.9 \pm 15.6
$AUC_{0-\infty, norm}^c$ (ng-h/mL)	37.4 \pm 12.1	38.5 \pm 11.5	37.8 \pm 11.5
$t_{1/2}$ (h)	12.7 \pm 3.2	13.6 \pm 3.6	13.1 \pm 3.3

^a $C_{max, norm}$ = Maximum plasma concentration observed, normalized to 70 kg body weight.

^b $AUC_{0-8, norm}$ = Area under the concentration-time curve from time zero to 8 hours, normalized to 70 kg body weight.

^c $AUC_{0-\infty, norm}$ = Area under the concentration-time curve from time zero to infinity, normalized to 70 kg body weight.

Conclusion: After the first topical ocular dose of moxifloxacin 0.5% ophthalmic solution, mean C_{max} was 1.2 ± 0.8 ng/mL. Following topical ocular dosing three times per day for four days, the mean steady-state peak plasma concentrations of moxifloxacin (Day 5) was 2.7 ± 1.3 ng/mL. This level of exposure is approximately 1600-times lower than the mean C_{max} reported ($4.5 \mu\text{g/mL}$) after well tolerated therapeutic oral dose of 400 mg. The estimated daily $AUC_{0-\infty}$ following topical administration to steady-state was $45 \text{ ng}\cdot\text{h/mL}$, which is approximately 1000-times lower than the value reported after the recommended 400 mg oral dose ($48 \mu\text{g}\cdot\text{h/mL}$). The estimated half-life of 13.1 ± 3.3 hours was similar to that reported in healthy subjects after oral and IV dosing. Maximum plasma concentrations and area under the plasma concentration-time curve were slightly higher in females than in the males; however, when normalized to body weight, these pharmacokinetic parameters were not significantly different between the groups. The pharmacokinetic parameters for Caucasian and Asian subjects were similar.

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