CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-598

MEDICAL REVIEW(S)

Medical Officer's Review of NDA [redacted] and NDA 21-598
Original/Pediatric Exclusivity

[redacted]

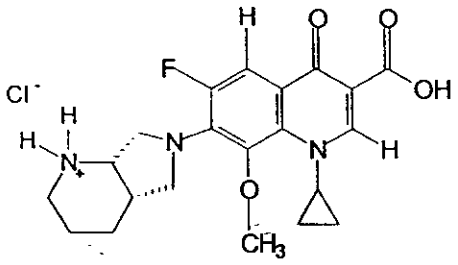
NDA 21-598
Medical Officer's Review

Submission Date: October 14, 2002
Review Completed: April 11, 2003

Proposed Trademark: To be determined

Generic Name: Moxifloxacin hydrochloride ophthalmic Solution, 0.5%

Chemical Name:



$C_{21}H_{24}FN_3O_4 \bullet HCl$ Mol Wt 437.9

Sponsor:

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Alcon Research, Ltd.
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Contact: Angela Kothe

Pharmacologic Category: Anti-infective (fluoroquinolone)

Related IND: [redacted]

Related NDAs:

NDA 21-085 Avelox Tablets (Bayer)
NDA 21-334 Avelox Tablets (Bayer)
NDA 21-277 Avelox IV Injection (Bayer)

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Executive Summary

1 Recommendations

1.1 Recommendation on Approvability

NDA 21-598 is recommended for approval for the treatment of bacterial conjunctivitis [redacted]

[redacted] is not recommended for approval for the treatment of [redacted].

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

No Phase 4 studies and/or risk management steps are recommended.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

Moxifloxacin hydrochloride is a "fourth" generation fluoroquinolone antibacterial agent. Oral moxifloxacin has been approved in more than 30 countries for the treatment of respiratory tract infections. In some countries, it is also approved for the treatment of uncomplicated skin and skin structure infections. In the United States, oral and injectable moxifloxacin have been approved for all the above mentioned indications. Ophthalmic moxifloxacin has not been approved by any regulatory agency in any country.

2.2 Efficacy

The submitted studies in NDA 21-598 are sufficient to establish efficacy for the use of moxifloxacin ophthalmic solution 0.5% in the treatment of bacterial conjunctivitis in patients older than 1 year of age.

The submitted study in [redacted] is not sufficient to establish efficacy for the use of moxifloxacin ophthalmic solution 0.5% in the treatment of [redacted]. The results of Study C-01-34 demonstrates that moxifloxacin ophthalmic solution 0.5% is not equivalent to Ciloxan ophthalmic solution 0.3% in clinical efficacy for this patient population.

2.3 Safety

The submitted studies in NDA 21-598 and [redacted] demonstrate an acceptable safety profile with the use of moxifloxacin ophthalmic solution 0.5% for the treatment of bacterial conjunctivitis. The most frequently reported adverse event is ocular discomfort.

2.4 Dosing

The dosing regimen proposed in NDA 21-598 and [redacted] is one drop three times a day [redacted], however, to achieve a greater reduction in bacterial load and no increased risk, the agency will propose treatment for 7 days.

2.5 Special Populations

No additional data on special populations are needed.

Clinical Review

1 Introduction and Background

1.1 Proposed Trademark: To be determined

Generic Name: Moxifloxacin hydrochloride ophthalmic solution, 0.5%

NDA Drug Classification: 3P/3S

Proposed Indication: Bacterial conjunctivitis

Dosage Form and
Route of Administration: Ophthalmic solution for topical ocular administration

Age Groups: [redacted]
Adults and pediatric patients older than one year of age

1.2 Moxifloxacin hydrochloride is a fourth generation fluoroquinolone antibacterial agent. There are four ophthalmic fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, and levofloxacin) that have been approved in the United States for use in the treatment of bacterial conjunctivitis in patients one year of age and older. There are currently no approved products to treat neonatal bacterial conjunctivitis.

1.3 There were no important milestones in the development of this product.

1.4 Oral moxifloxacin has been approved in more than 30 countries including the United States, Canada, Spain, Germany, and Italy for the treatment of respiratory tract infections such as community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, and acute bacterial sinusitis. In some countries, it is also approved for the treatment of uncomplicated skin and skin structure infections. In the United States, oral and injectable moxifloxacin have been approved for all of the above mentioned indications.

1.5 There are no safety and effectiveness concerns associated with agents in this pharmacologic class.

2 Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

Agree with Chemistry and Animal Pharmacology and Toxicology recommendations. See Chemistry and Animal Pharmacology and Toxicology Reviews for detailed results.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

Agree with Clinical Pharmacology and Biopharmaceutics Review. See Review for detailed results.

3.2 Pharmacodynamics

Agree with Clinical Pharmacology and Biopharmaceutics Review. See Review for detailed results.

4 Description of Clinical Data and Sources

4.1 Included in this medical officer's review are evaluations of four clinical trials, three conducted in the United States and one conducted in India. Protocols C-00-55, C-00-46, and C-01-34 contribute to the efficacy and safety database. Protocol C-00-02 contributes to the safety database, but is not the primary support of efficacy

4.2 See Table 1 for a descriptive summary of the clinical trials.

Table 1 – Description of Clinical Data Sources

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized/ Completed	Status
Phase III Studies								
Safety and efficacy C-00-02 U.S.	Multi-center, randomized, double-blinded, parallel group, vehicle-controlled	3 days	Adults and pediatric patients ≥ 1 year of age with suspected bacterial conjunctivitis	Moxifloxacin 0.5% Moxifloxacin 0.5% Vehicle Vehicle	1 drop BID OU for 3 days 2 drops BID OU for 3 days 1 drop BID OU for 3 days 2 drops BID OU for 3 days	20 U.S.	140/128 (1:1:1:1)	Completed
Safety and efficacy C-00-55 U.S.	Multi-center, randomized, double-blinded, parallel group, vehicle-controlled	4 days	Adults and pediatric patients > 1 month of age with suspected bacterial conjunctivitis	Moxifloxacin 0.5% Vehicle	1 drop TID OU for 4 days 1 drop TID OU for 4 days	37 U.S.	544/460 (1:1)	Completed
Safety and efficacy C-00-46 India	Multi-center, randomized, double-blinded, parallel group, active-controlled	4 days	Adults and pediatric patients ≥ 1 year of age with suspected bacterial conjunctivitis	Moxifloxacin 0.5% Ocuflox 0.3%	1 drop TID OU for 4 days 1 drop QID OU for 4 days	15 India	554/485 (1:1)	Completed
Pediatric Study								
Safety and efficacy C-01-34 U.S.	Multi-center, randomized, double-blinded, parallel group, active-controlled	4 days	Neonates from birth to 1 month of age with presumed bacterial conjunctivitis	Moxifloxacin 0.5% Ciloxan 0.3%	1 drop TID OU for 4 days 1 drop TID OU for 4 days	32 U.S.	209/201 (1:1)	Completed

Reviewer's Comments:

Studies C-00-55 and C-00-46 are the primary support of efficacy for patients older than one month of age and contribute to the safety database for this patient population. Study C-01-34 [redacted] *contributes to the safety database for this patient population. Study C-00-02 contributes to the determination of the optimal dosing regimen.*

4.3 No post-marketing data are available. Ophthalmic moxifloxacin has not been approved by any regulatory agency in any country.

4.4 There are not any data in the published literatures that are pertinent to the review of this submission.

5 Clinical Review Methods

5.1 This medical officer's review evaluated each of the four clinical trials separately.

5.2 The submission is provided in paper format. The review relied on the paper copy.

5.3 The Division of Scientific Investigations plans to audit [redacted] for protocol C-00-55 and [redacted] for protocol C-01-34).

5.4 There is no evidence to indicate that the trials were not conducted in accordance with accepted ethical standards.

5.5 Financial disclosure statements are submitted. There is no evidence to indicate that participation of investigators who have financial arrangements with the applicant affected the integrity of the findings.

6 Integrated Review of Efficacy

6.1 The submitted studies in NDA21-598 are sufficient to establish efficacy for the use of moxifloxacin ophthalmic solution 0.5% in the treatment of bacterial conjunctivitis of susceptible microorganisms in patients older than 1 year of age.

The submitted study in [redacted] is not sufficient to establish efficacy for the use of moxifloxacin ophthalmic solution 0.5% in the treatment of [redacted]

6.2 The efficacy database consisted of one clinical trial conducted in India in support of efficacy in patients ages 1 year and older, one trial conducted in the United States [redacted] in patients ages 1 month and older, and one trial conducted in the United States in [redacted] in neonates ages 0 to 1 month.

6.3.1 Proposed Indication #1: Bacterial conjunctivitis [redacted]

Study #1 **Protocol No. C-00-55** **Conducted 6/28/01 to 8/5/02**

Title: An Evaluation of the Safety and Efficacy of Moxifloxacin Ophthalmic Solution 0.5% Versus Moxifloxacin Vehicle in the Treatment of Bacterial Conjunctivitis

Study Design: A multi-center, randomized, double-blinded, vehicle-controlled, parallel group study.

Test Drug Schedule: Patients received one drop of masked study medication in both eyes three times a day for four days.

Investigator Number	Investigator	Number Randomized	
		MOXFX	Vehicle
2355	Wilson P. Andrews, Jr., M.D. Marietta, GA 30062 USA	14	13
3288	Syed Saifuddin Azhar, M.D. Galeston TX 77555 USA	6	7
2377	Robert Bettis. M.D. Edmonds, WA 98026 USA	18	18
362	Delmar R. Caldwell, M.D. New Orleans, LA 70112 USA	1	1
3509	Robert J. Carson, M.D. Cincinnati, OH 45245 USA	10	10
2833	Shane G. Christensen, M.D. Salt Lake City, UT 84121 USA	18	18
3452	Ralph M. Conti, M.D. Henderson, NV 89014 USA	0	0
2955	Dick N. Creager, M.D. Salt Lake City, UT 84121 USA	18	18
3501	Eleuterio P. Delfin, Jr., M.D.	18	18

NDA 21-598 and ——— ; moxifloxacin hydrochloride ophthalmic solution 0.5%

		Number Randomized	
	Paramount, CA 90723 USA		
3545	**Liberation De Leon, M.D.**	16	16
	Paramount, CA 90723 USA		
3064	**Bruce C. Douglas, M.D.**	11	11
	Portland, OR 97216 USA		
3108	**John M. Gilbert, Jr., M.D.**	0	0
	Fullerton, CA 92835 USA		
3033	**Keith Harrington, M.D.**	18	18
	South Jordan, UT 84095 USA		
3491	**William P. Jennings, M.D.**	0	0
	San Antonio, TX 78229 USA		
845	**Harold R. Katz, M.D.** Baltimore, MD 21215 USA	5	5
3061	**Theodore M. Lee, M.D.**	2	2
	Atlanta, GA 30309 USA		
3531	**Keith Luther, M.D.**	0	1
	Edmonds, WA 98026 USA		
498	**James P. McCulley, M.D.** Dallas, TX 75390 USA	2	3
3488	**Issac R. Melamed, M.D.**	4	3
	Englewood, CO 80112 USA		
3478	**Daniel J. Monahan, M.D.**	2	3
	Pittsburgh, PA 15215 USA		
3360	**Sara Murdoch, M.D.**	7	7
	Olympia, WA 98506 USA		
2339	**Robert B. Nett, Jr., M.D.**	2	3
	San Antonio, TX 78229 USA		
3489	**Corazon I. Oca, M.D.**	17	17
	Fountain Valley, CA 92708 USA		
3359	**Carl R. Ott, M.D.**	0	0
	Lacey, WA 98516 USA		
2542	**Bruce J. Pistorius, M.D.**	12	12
	Shreveport, LA 71105 USA		
3042	**Albert J. Razzetti, M.D.**	0	0

		Number Randomized	
	DeLand, FL 32720 USA		
3109	Dennis S. Riff, M.D. Santa Ana, CA 92701 USA	7	7
2387	Gilbert R. Salazar, M.D. San Antonio, TX 78205 USA	5	5
3169	Tommy J. Schechtman, M.D. Palm Beach Gardens, FL 33410 USA	4	4
3069	Gerald R. Schockey, M.D. Mesa, AZ 85201 USA	10	10
3520	Henry P. Sideropoulos, M.D. Pasadena, CA 91105 USA	17	17
3130	Ronald Sockolov, M.D. Sacramento, CA 95825 USA	7	7
3499	Malcolm J. Sperling, M.D. Fountain Valley, CA 92708 USA	3	3
271	Robert H. Stewart, M.D. Houston, TX 77052 USA	5	6
3533	Lori J. Tindel-Kahn, M.D. White Plains, NY 10604 USA	2	2
3168	Michael W. Warren, M.D. Lancaster, PA 17601 USA	1	2
3485	Michael F. Yeiser, M.D. Owensboro, KY 42303 USA	8	7

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

Study Design

This was a multi-center, randomized, double-blinded, vehicle-controlled, parallel group study designed to evaluate the safety and efficacy of moxifloxacin ophthalmic solution

0.5% (MOXFX) compared to vehicle of MOXFX (Vehicle) for the treatment of bacterial conjunctivitis in adults and children older than one month of age.

Eligible patients who met all inclusion/exclusion criteria were randomized to receive MOXFX or Vehicle (1:1) for four days. Patients were instructed to instill one drop of masked study medication in both eyes three times per day while awake on Days 1 through 4. The patients were evaluated at Visit 1 (Day 1), Visit 2 (Day 3±1), Visit 3 (Day 5±1), Visit 4 (Day 9±1). At each visit, patients underwent routine ophthalmic exams, including visual acuity and biomicroscopy. Ocular bacteriological cultures and fundus exams were performed at Visit 1 and at the time a patients exited from the study (Exit Visit). Ocular viral cultures were obtained at Visit 1 and at the Exit Visit if the patient exited the study as a treatment failure. Investigators rated the ocular signs for both eyes at Visits 2, 3, and 4.

Study Medications

- Moxifloxacin ophthalmic solution 0.5% (Lot # 00-500221-1, Formulation Identification # 101149)
- Non-preserved Moxifloxacin Vehicle (Lot # 00-500202-1, Formulation Identification # 101611)

Inclusion Criteria

Patients can be included only if they meet all the following criteria:

1. Patients greater one (1) month of age, any race and either sex.
2. Have a diagnosis of bacterial conjunctivitis based on clinical observation. All patients must have a rating ≥ 1 for bulbar conjunctival injection and a rating ≥ 1 for conjunctival discharge/exudate at the Day 1 visit.
3. Must be able to understand and sign an informed consent form that has been approved by an institutional Review Board/Independent Ethics Committee. If the patient is under 18 years of age, the informed consent must be understood and signed by the patient's legally authorized representative (parent or guardian). Assent to participate in the study should be obtained from patients over 6 and under 18 years of age.
4. Must agree to comply with the visit schedule and other requirements of the study. The parent or guardian must agree to ensure compliance of patients less than 18 years of age.
5. Males, or females who are not pregnant and are not lactating. All females of childbearing potential (those who are not premenstrual, not postmenopausal or surgically sterile) may participate only if they have a negative urine pregnancy test prior to randomization, and if they agree to use adequate birth control methods to prevent pregnancy throughout the study. Adequate birth control methods include hormonal-oral, implantable or injectable contraceptives; mechanical-spermicide in conjunction with a

barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner.

Exclusion Criteria

Patient with any of the following conditions are not eligible for participation in this clinical trial:

1. Contact lens wear during the course of the study.
2. Patients with only one sighted eye or vision not correctable to 0.6 LogMAR or better in either eye using ETDRS chart or 20/80 (Snellen acuity) or better in either eye using other age-appropriate measurement method in accordance with the American Academy of Pediatrics Eye Examination and Vision Screening in Infants, Children, and Young Adults Policy Statement. The American Academy of Pediatrics Recommendations for Preventive Pediatric Health Care states that formal vision screening should begin at 3 years of age. Visual acuity measurement may be attempted for children under 3 at the discretion of the investigator. If not conducted, the child must be able to fix and follow. Visual acuity is to be measured using the same method for each patient at each visit.
3. Abnormal findings in the posterior pole of the retina or any media opacity on fundus examination at the Day 1 (Screening/Baseline) visit.
4. Presence of active inflammation and/or active structural change in the cornea, iris, or anterior chamber at the Day 1 (Screening/Baseline) visit.
5. Suspected fungal, viral (e.g., Herpes Simplex) or Acanthamoeba infection, based on clinical observation.
6. Use of any preserved topical ocular mediations at the time of entry into the study or during study participation. No-preserved tear substitutes are allowed.
7. Use of any topical ocular antibacterial within the past 24 hours or during study participation.
8. Use of any oral antibacterial within the past 72 hours or during study participation.
9. Known or suspected allergy or hypersensitivity to fluoroquinolones.
10. Any systemic or ocular disease or disorder, complicating factors or structural abnormality that would negatively affect the conduct or outcome of the study (e.g., hepatitis, acute or chronic renal insufficiency).
11. Use of systemic steroids within 14 days prior to study entry. Use of topical ocular steroids or nonsteroidal anti-inflammatories (NSAIDs), within one week prior to study entry. Use of these medications is not allowed any time during the study. Bronchial inhaled steroids are allowed.
12. Use of systemic nonsteroidal anti-inflammatories (NSAIDs) within 24 hours prior to study entry or any time during the study unless the patient has been on a steady (not as needed) treatment regimen for at least 2

months prior to entry and the therapy will continue throughout the study. Acetaminophen (e.g., Tylenol) is allowed.

13. Pregnant or lactating women, women who have a positive urine pregnancy test, or women of childbearing potential who are not using adequate birth control to prevent pregnancy.
14. Participation in any other investigational clinical study within 30 days prior to study enrollment.
15. Any current immunosuppressive disorder (e.g., HIV-positive), or use of immunosuppressive therapy (including chemotherapy).
16. Any patient previously enrolled in this study.
17. Any patient who is on staff at the investigational site or is a family member of staff personnel.

Additionally, the Medical Monitor may declare any patient ineligible for a sound medical reason.

Efficacy Variables

The primary clinical efficacy variable was the clinical cure rate (i.e., the sum of the ratings for bulbar conjunctival injection and conjunctival discharge/exudate is zero) at the test-of-cure visit (Day 9). The primary microbiological efficacy variable was the eradication rate of ocular pathogens at the test-of-cure visit (Day 9).

Secondary clinical efficacy variables included ocular signs (i.e., lid erythema, lid swelling, palpebral conjunctiva) and ocular symptoms (i.e., foreign body sensation, tearing, and photophobia).

Reviewer's Comments:

The agency did not agree with the primary clinical efficacy variable as stated in the protocol. The primary clinical efficacy variable utilized in the review of this NDA is the assessment of the clinical cure rate (i.e., the sum of the ratings for bulbar conjunctival injection and conjunctival discharge/exudate is zero) at Day 5 (end-of-therapy).

Safety Variables

The following safety variables were assessed:

1. Visual acuity
2. Biomicroscopy (cornea and iris/anterior chamber)
3. Fundus exam
4. Adverse events

Study Plan

Parameters	Day 1 Screening/ Baseline	Day 3 (±1day)	Day 5 (+1day) End-of-Therapy	Day 9 (±1day) Test-of-Cure	Exit Procedures[a]	Ophthalmologist Exit Visit[h]
Screen for inclusion/exclusion criteria	X					
Informed consent	X					
General information; Medical history	X					
Pregnancy test[b]	X				X	
Changes in concomitant medication or general health		X	X	X		X
Patients rate ocular symptoms	X	X	X	X		
Visual acuity	X	X	X	X		X
Investigators rate ocular signs	X	X	X	X		X
Evaluation of cornea and iris/anterior chamber (slit lamp and/or penlight or ophthalmoscope)	X	X	X	X		X
Collect ocular bacteriological culture[c]	X				X	
Collect ocular viral specimen	X				X[d]	
Fundus exam of posterior pole (dilated and/or undilated)	X				X	X
Dispense medication	X	X[e]				
Dose study medication (in-office)	X					
Collect study medication		X	X		X	
Record adverse events	X	X	X	X		X
Complete exit form[g]					X	

[a] At any time a patient exited from the study. [b] For women of childbearing potential, before instillation of drug and at exit from the study. [c] At Day 1 and at any time a patient exited from the study. [d] At Day 1 and if patient exited the study as a treatment failure. [e] As needed. [f] After dosing. [g] At any time a patient exited from the study. [h] This visit applied to those patients who had not been examined by an ophthalmologist at the exit visit.

Subject Disposition and Demographics

All 544 randomized subjects received treatment and 460 subjects completed the study.

Subject Disposition

	Number of Subjects		
	MOXFX N (%)	Vehicle N (%)	Total N (%)
Randomized	270	274	544
Discontinued prematurely	25 (9.3)	40 (14.6)	65 (11.9)
Included in safety evaluations	270 (100.0)	274 (100.0)	544 (100.0)
Included in intent-to-treat efficacy analysis	270 (100.0)	274 (100.0)	544 (100.0)
Included in modified intent-to-treat efficacy analysis	143 (53.0)	144 (52.6)	287 (52.8)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Reason
271	106	MOXFX	Lost to follow-up
498	304	Vehicle	Treatment failure
2339	601	Vehicle	Lost to follow-up
	603	Vehicle	Treatment failure
2355	701	Vehicle	Treatment failure
	713	MOXFX	Adverse event - pneumonia
	719	MOXFX	Adverse event – otitis media
2377	801	Vehicle	Treatment failure
	804	MOXFX	Treatment failure
	807	Vehicle	Noncompliance
2387	3402	MOXFX	Lost to follow-up
	3403	MOXFX	Noncompliance
	3404	Vehicle	Treatment failure
	3407	Vehicle	Treatment failure
	3408	MOXFX	Lost to follow-up
2542	904	MOXFX	Adverse event - keratoconjunctivitis
	915	Vehicle	Adverse event - infection
	917	MOXFX	Adverse event -- otitis media
2833	1023	Vehicle	Treatment failure
	1027	Vehicle	Treatment failure
	1031	MOXFX	Treatment failure
2955	1106	Vehicle	Treatment failure
	1108	MOXFX	Treatment failure
	1109	Vehicle	Treatment failure
	1114	Vehicle	Treatment failure
	1122	Vehicle	Other eye infected
	1130	MOXFX	Treatment failure
	1134	MOXFX	Treatment failure
3033	1203	Vehicle	Adverse event - infection
	1205	Vehicle	Treatment failure
	1214	Vehicle	Treatment failure
	1217	Vehicle	Adverse event - hordeolum
	1222	MOXFX	Treatment failure
	1230	MOXFX	Treatment failure
3061	1401	Vehicle	Treatment failure
3069	1603	MOXFX	Treatment failure
	1609	Vehicle	Treatment failure
	1612	Vehicle	Patient decision
3069	1615	MOXFX	Lost to follow-up
	1616	Vehicle	Treatment failure
3109	1901	Vehicle	Adverse events -- erythema multiforme, dermatitis, pharyngitis
	1902	MOXFX	Treatment failure
	1906	MOXFX	Treatment failure
	1909	MOXFX	Treatment failure
	1912	Vehicle	Treatment failure
	1914	MOXFX	Treatment failure
3130	2110	Vehicle	Patient decision
3168	2603	Vehicle	Treatment failure
3288	2210	Vehicle	Lost to follow-up
	2211	Vehicle	Lost to follow-up
	2213	Vehicle	Lost to follow-up
3485	2807	Vehicle	Adverse event – otitis media
3489	3208	Vehicle	Patient decision
3499	3004	Vehicle	Treatment failure
3501	3113	Vehicle	Adverse event - iritis

Investigator	Patient	Treatment	Reason
	3122	MOXFX	Adverse events -- accidental injury, subconjunctival hemorrhage
	3123	Vehicle	Adverse event – infection
	3132	MOXFX	Noncompliance
3509	3310	Vehicle	Treatment failure
3520	3512	MOXFX	Lost to follow-up
	3520	Vehicle	Lost to follow-up
	3521	MOXFX	Lost to follow-up
	3522	Vehicle	Adverse event – hypokalemia
3533	3701	Vehicle	Treatment failure
3545	3817	Vehicle	Lost to follow-up

Summary of Demographics

	Modified Intent-to-Treat			Intent-to-Treat		
	MOXFX	Vehicle	P-value[a]	MOXFX	Vehicle	P-value[a]
Number of Patients:	143	144		270	274	
AGE			0.6538			0.9632
MEAN(SD)	16.3(18.6)	15.3(19.5)		18.9(18.7)	19.0(19.0)	
MIN-MAX	0-77	0-85		0-89	0-85	
0-12 years	83 (58.0)	97 (67.4)	0.1918	140 (51.9)	140 (51.1)	0.9826
>12 <65 years	56 (39.27)	42 (29.2)		122 (45.2)	126 (46.0)	
≥65 years	4 (2.8)	5 (3.5)		8 (3.0)	8 (2.9)	
SEX: N (%)			0.0861			0.2486
Female	82 (57.3)	68 (47.2)		162 (60.0)	151 (55.1)	
Male	61 (42.7)	76 (52.8)		108 (40.0)	123 (44.9)	
RACE: N (%)			0.6036			0.9968
Caucasian	79 (55.2)	79 (54.9)		168 (62.2)	171 (62.4)	
Black	11 (7.7)	6 (4.2)		17 (6.3)	16 (5.8)	
Asian	4 (2.8)	5 (3.5)		9 (3.3)	9 (3.3)	
Other	49 (34.3)	54 (37.5)		76 (28.1)	78 (28.5)	

[a] P-value for age based on analysis of variance. P-values for age range, sex, and race based on Chi-square test of independence (or Fishers Exact test if N<5).

Demographic Table – Age Range <18 Years

	Modified Intent-to-Treat			Intent-to-Treat		
	Treatment			Treatment		
Age	MOXFX N=143 N (%)	Vehicle N=144 N (%)	P-value[a]	MOXFX N=270 N (%)	Vehicle N=274 N (%)	P-value[a]
1-23 months	21 (23.3)	24 (24.2)	0.1443	24 (8.9)	29 (10.6)	0.5057
2-11 years	60 (66.7)	72 (72.7)		109 (40.4)	108 (39.4)	
12-17 years	9 (10.0)	3 (3.0)		23 (8.5)	17 (6.2)	

[a] Chi-square test of independence (or Fishers Exact test if N<5).

Efficacy

Summary of Clinical Cure and Microbial Eradication by Study Day

Study Day **Modified Intent-to-Treat (MITT[c])**	Outcome	MOXFX	Vehicle	P-value[a]
Day 3	Clinical cure	27% (38/143)	15% (22/144)	0.0186
Day 5 (end-of-therapy)	**Clinical cure**	**66% (95/143)**	**51% (74/144)**	**0.0096***
Day 9 (test-of-cure)	Clinical cure	83% (113/137)	74% (101/136)	0.0991
	Microbial eradication	**82% (11/136)**	**67% (93/138)**	**0.0069***
Study Day **Intent-to-Treat (ITT[b])**	Outcome	MOXFX	Vehicle	P-value[a]
Day 3	Clinical cure	29% (78/270)	20% (54/274)	0.0125
Day 5 (end-of-therapy)	**Clinical cure**	**62% (167/270)**	**52% (142/274)**	**0.0182***
Day 9 (test-of-cure)	Clinical cure	77% (201/260)	72% (187/259)	0.1805

[a] Chi-square test of independence (or Fishers Exact test if N<5). [b] ITT=All patients who received treatment and had at least one on-therapy visit. Patients who had no measurements after baseline were included as treatment failures. [c] MITT=All patients who received treatment, had at least one on-therapy visit, met inclusion/exclusion criteria, and were culture positive for bacteria on Day 1. Patients who had no measurements after baseline were included as treatment failures. * $p<0.05$. In favor of MOXFX.

Reviewer's Comments:

The study populations that are utilized in the review of Study C-00-55 to establish primary clinical and microbiological efficacy are the modified intent-to-treat and intent-to-treat populations.

MOXFX dosed three times a day demonstrates superiority to its vehicle in clinical and microbiological efficacy (p=0.0096 and p=0.0069, respectively). The clinical cure rate for MOXFX is 66%. The microbiologic eradication rate for MOXFX is 82%.

Microbial Eradication Rates from Baseline to Final by Organism

Organism	MOXFX	Vehicle
GRAM-POSITIVE BACTERIA		
Staphylococcus epidermidis	91% (21/23)	89% (17/19)
Streptococcus pneumoniae	85% (17/20)	63% (17/27)
Staphylococcus aureus	100% (16/16)	56% (5/9)
Staphylococcus hominis	100% (6/6)	
Staphylococcus capitis	100% (3/3)	
Staphylococcus saprophyticus	100% (1/1)	
Streptococcus "schlechii"	100% (1/1)	
Streptococcus parasanguinis subsp. A	100% (1/1)	
Streptococcus salivarius	100% (1/1)	
Streptococcus sanguis subsp. nov.	100% (1/1)	

Streptococcus sp. nov. 6	100% (1/1)	
Streptococcus viridans group sp. nov. F	100% (1/1)	
Streptococcus viridans group sp. nov. M	100% (1/1)	
Streptococcus viridans group sp. nov. W	100% (1/1)	
Streptococcus mitis	100% (1/1)	
Corynebacterium argentoratense	100% (1/1)	
Kocuria kristinae	100% (1/1)	
GRAM-NEGATIVE BACTERIA		
Haemophilus influenzae	75% (21/28)	71% (22/31)
Haemophilus parainfluenzae	100% (5/5)	
Haemophilus sp. nov. "*alconae*"		75% (6/8)
Leclercia adecarboxylata	100% (1/1)	
Pseudomonas aeruginosa	100% (1/1)	
Serratia marcescens	100% (1/1)	

Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline.

Reviewer's Comments:

The Division of Scientific Investigations (DSI) identified discrepancies between the microorganisms reported by the central microbiology laboratory and the applicant's database. This was reported for multiple investigation sites participating in protocols C-00-55, C-00-46, and C-01-34. Applicant's explanation of the discrepancies was that they reflected the differences between the preliminary identification of organisms by the central microbiology laboratory and the definitive identification by the applicant's own microbiology laboratory. It is the current policy of CDER that the applicant should not act as its own central laboratory. An independent central laboratory should confirm differences. For this submission, the agency considers the microorganisms identified by the central laboratory to be definitive. The microorganisms listed for the MOXFX treatment group in the above table includes only those organisms identified by the central laboratory.

Microbiological efficacy is demonstrated primarily against Haemophilus influenzae, Staphylococcus epidermidis, Streptococcus pneumoniae, and Staphylococcus aureus.

Study #2 **Protocol No. C-00-46** **Conducted 8/17/01 to 3/9/02**

Title: An Evaluation of the Safety and Efficacy of Moxifloxacin Ophthalmic Solution 0.5% Versus Ocuflox Ophthalmic Solution 0.3% in the Treatment of Bacterial Conjunctivitis in India

Study Design: A multi-center, double-blinded, active-controlled, parallel group study.

Test Drug Schedule: Patients were randomized into one of two treatment groups: Moxifloxacin ophthalmic solution 0.5% one drop three times a day in both eyes for four days or Ocuflox ophthalmic solution 0.3% one drop four times a day in both eyes for four days.

Investigator Number	Investigator	Number Randomized	
		MOXFX	OCUFX
3050	Ravindra R. Battu M.B.B.S. M.S. (Ophthalmology)	10	9
3051	Yasmin R. Bhagat M.B.B.S. D.O.M.S. M.S. (ophthalmology)	32	33
3070	Balasubraminiam Ganesh M.B.B.S. D.O.M.S. M.S. (Ophthalmology)	19	19
3071	Prashant Garg M.B.B.S. M.S. (Ophthalmilogy)	8	8
3053	Nelson C.A. Jesudasan M.B.B.S. D.O.M.S. M.Surg (Ophthalmology)	29	29
3054	Shreekant B. Kelkar M.B.B.S. D.O.M.S. M.S. (Ophthalmology)	27	25
3055	Thomas Kuriakose M.B.B.S. F.R.C.S. (Ophthalmology)	14	14
3072	Hajib Narahari Madhavan M.B.B.S. F.R.C.S. (Ophthalmology) Ph.D.	8	8
3073	Dinas K. Mehta M.B.B.S. M.S. (Ophthalmology)	8	10
3056	Shanta A. Motwane M.B.B.S. M.S. (Ophthalmology)	25	25
3074	Gyanam G. Murthy M.B.B.S. M.S. (Ophthalmology)	25	25
3057	Vir B. Pratap M.B.B.S. M.S. (Ophthalmology)	14	15
3075	Manjunath Srinivasan M.B.B.S. M.S. (Ophthalmology)	26	26
3058	Rasik B. Vajpayee M.B.B.S. M.S. (Ophthalmology)	7	6
3059	Usha H. Vyas M.B.B.S. M.S. (Ophthalmology)	25	25

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

Study Design

The study design was identical to that of Study #1 except for the following differences:

1. The study was conducted in India.
2. The study population consisted of patients one year of age and older.
3. Moxifloxacin ophthalmic solution 0.5% (MOXFX) was compared to an active-control, Ocuflox 0.3% (OCUFX).

Study Medications

- Moxifloxacin ophthalmic solution 0.5% (Lot # 00-500221-1, Formulation Identification # 101149)
- Ocuflox ophthalmic solution 0.3% (Lot # 00-500217-1, Formulation Identification # 95756)

Efficacy Variables

The primary clinical, primary microbiological, and secondary clinical efficacy variables were the same as in Study #1.

Safety Variables

The safety variables were the same as in Study #1.

Reviewer's Comments:

The agency did not agree with the primary clinical efficacy variable as stated in the protocol. The primary clinical efficacy variable utilized in the review of this NDA is the assessment of the clinical cure rate (i.e., the sum of the ratings for bulbar conjunctival injection and conjunctival discharge/exudate is zero) at Day 5 (end-of-therapy).

Subject Disposition and Demographics

All 554 randomized subjects received treatment and 485 subjects completed the study.

Subject Disposition

	Number of Subjects		
	MOXFX N (%)	OCUFX N (%)	Total N (%)
Randomized	277	277	554
Discontinued prematurely	27 (9.7)	42 (15.2)	69 (12.5)
Included in safety evaluations	277 (100.0)	277 (100.0)	554 (100.0)
Included in intent-to-treat efficacy analysis	270 (100.0)	274 (100.0)	544 (100.0)
Included in modified intent-to-treat efficacy analysis	176 (63.5)	168 (60.6)	344 (62.1)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Reason
3050	1001	OCUFX	Lost to follow-up
	1006	OCUFX	Treatment failure
	1009	OCUFX	Lost to follow-up
	1014	OCUFX	Treatment failure
3051	2004	OCUFX	Lost to follow-up
	2038	OCUFX	Treatment failure
	2039	MOXFX	Patient decision
	2046	OCUFX	Treatment failure
3053	4013	OCUFX	Treatment failure
	4014	MOXFX	Treatment failure
	4029	OCUFX	Lost to follow-up
	4039	OCUFX	Treatment failure
	4041	OCUFX	Treatment failure
3054	5004	OCUFX	Lost to follow-up
	5007	OCUFX	Patient decision
	5010	OCUFX	Non-compliance
	5011	MOXFX	Lost to follow-up
	5017	MOXFX	Treatment failure
	5021	MOXFX	Lost to follow-up
	5043	MOXFX	Lost to follow-up
	5052	MOXFX	Lost to follow-up
3055	6004	OCUFX	Lost to follow-up
3056	7010	MOXFX	Lost to follow-up
3057	8006	OCUFX	Lost to follow-up
	8012	OCUFX	Lost to follow-up
	8014	MOXFX	Lost to follow-up
	8017	OCUFX	Lost to follow-up
	8028	OCUFX	Lost to follow-up
3058	9006	OCUFX	Treatment failure
	9011	OCUFX	Patient decision
3059	9101	OCUFX	Treatment failure
	9105	MOXFX	Treatment failure
	9107	OCUFX	Adverse events – dacryocystitis, diabetes mellitus
	9109	OCUFX	Adverse event - keratitis
	9111	MOXFX	Lost to follow-up
	9116	OCUFX	Lost to follow-up
	9117	OCUFX	Treatment failure
	9124	OCUFX	Treatment failure
	9129	OCUFX	Treatment failure
	9132	MOXFX	Treatment failure
	9133	OCUFX	Treatment failure
	9146	MOXFX	Treatment failure
3070	9206	OCUFX	Treatment failure
	9212	OCUFX	Treatment failure
	9217	MOXFX	Treatment failure
	9220	MOXFX	Treatment failure
3071	9303	MOXFX	Treatment failure
	9304	OCUFX	Lost to follow-up
	9311	OCUFX	Treatment failure
	9312	MOXFX	Treatment failure
3072	9401	MOXFX	Treatment failure
	9404	OCUFX	Treatment failure
	9414	MOXFX	Lost to follow-up
3073	9503	MOXFX	Lost to follow-up
	9509	MOXFX	Lost to follow-up
3074	9611	OCUFX	Lost to follow-up
	9613	MOXFX	Lost to follow-up
	9622	MOXFX	Lost to follow-up

Investigator	Patient	Treatment	Reason
	9624	OCUFX	Lost to follow-up
	9631	OCUFX	Lost to follow-up
	9645	OCUFX	Lost to follow-up
3075	9707	MOXFX	Lost to follow-up
	9708	MOXFX	Lost to follow-up
	9714	MOXFX	Treatment failure
	9717	OCUFX	Treatment failure
	9734	OCUFX	Treatment failure
	9735	MOXFX	Treatment failure
	9736	OCUFX	Treatment failure
	9740	OCUFX	Treatment failure

Summary of Demographics

	Modified Intent-to-Treat			Intent-to-Treat		
	MOXFX	OCUFX	P-value[a]	MOXFX	OCUFX	P-value[a]
Number of Patients:	176	168		277	277	
AGE			0.6538			0.5096
MEAN(SD)	36.9(19.0)	38.3(18.2)		36.6(18.7)	37.6(18.4)	
MIN-MAX	1-85	1-78		1-85	1-78	
0-12 years	17 (9.7)	14 (8.3)	0.7487	24 (8.7)	26 (9.4)	0.9565
>12 <65 years	140 (79.5)	139 (82.7)		227 (81.9)	225 (81.2)	
≥65 years	19 (10.8)	15 (8.9)		26 (9.4)	26 (9.4)	
SEX: N (%)			0.4518			0.6467
Female	49 (27.8)	53 (31.5)		84 (30.3)	89 (32.1)	
Male	127 (72.2)	115 (68.5)		193 (69.7)	188 (67.9)	
RACE: N (%)			N/A			N/A
Asian	176 (100.0)	168 (100.0)		277 (100.0)	277 (100.0)	

[a] P-value for age based on analysis of variance. P-values for age range, sex, and race based on Chi-square test of independence (or Fishers Exact test if N<5).

Demographic Table – Age Range <18 Years

	Modified Intent-to-Treat			Intent-to-Treat		
	Treatment			Treatment		
Age	MOXFX N=176 N (%)	OCUFX N=168 N (%)	P-value[a]	MOXFX N=277 N (%)	OCUFX N=277 N (%)	P-value[a]
1-23 months	4 (2.3)	1 (0.6)	0.4391	4 (1.4)	4 (1.4)	0.3098
2-11 years	13 (7.4)	13 (7.7)		20 (7.2)	21 (7.6)	
12-17 years	8 (4.5)	4 (2.4)		14 (5.1)	6 (2.2)	

[a] Chi-square test of independence (or Fishers Exact test if N<5).

Efficacy

Summary of Clinical Cure and Microbial Eradication by Study Day

Study Day Modified Intent-to-Treat (MITT[a])	Outcome	MOXFX	OCUFX	Confidence Interval	P-value[a]
Day 3	Clinical cure	21% (36/176)	20% (34/168)	-8% to 9%	0.9602

Day 5 (end-of-therapy)	**Clinical cure**	**69% (122/176)**	**68% (114/168)**	**-8% to 11%**	**0.7704**
Day 9 (test-of-cure)	Clinical cure	87% (153/176)	84% (141/168)	-4% to 10%	0.4295
	Microbial eradication	**94% (157/168)**	**89% (141/159)**		**0.1291**
Study Day **Intent-to-Treat (ITT[b])**	Outcome	MOXFX	OCUFX		P-value[a]
Day 3	Clinical cure	23% (64/277)	20% (55/277)		0.3518
Day 5 (end-of-therapy)	Clinical cure	69% (190/277)	68% (188/277)		0.8552
Day 9 (test-of-cure)	Clinical cure	86% (239/277)	83% (230/277)		0.2887

[a] Chi-square test of independence (or Fishers Exact test if N<5). [b] ITT=All patients who received treatment and had at least one on-therapy visit. Patients who had no measurements after baseline were included as treatment failures. [c] MITT=All patients who received treatment, had at least one on-therapy visit, met inclusion/exclusion criteria, and were culture positive for bacteria on Day 1. Patients who had no measurements after baseline were included as treatment failures.

Reviewer's Comments:

The study population that is utilized in the review of Study C-00-46 to establish primary clinical and microbiological efficacy is the modified intent-to-treat populations.

MOXFX dosed three times a day appears to be equivalent to OCUFX dosed four times a day in clinical and microbiological efficacy. The clinical cure rate for MOXFX is 69% and 68% for OCUFX. The microbiologic eradication rate for MOXFX is 94% and 89% for OCUFX.

Microbial Eradication Rates from Baseline to Final by Organism

Organism	MOXFX	OCUFX
GRAM-POSITIVE BACTERIA		
Streptococcus pneumoniae	100% (7/7)	
Staphylococcus aureus	100% (21/21)	100% (13/13)
Staphylococcus epidermidis	100% (22/22)	98% (43/44)
Staphylococcus haemolyticus	94% (16/17)	100% (10/10)
Staphylococcus hominis	100% (5/5)	56% (5/9)
Staphylococcus intermedius	100% (1/1)	
Staphylococcus saprophyticus		100% (5/5)
Micrococcus luteus	100% (5/5)	
Staphylococcus warneri	100% (3/3)	
Streptococcus pyogenes	100% (2/2)	
Corynebacterium amycolatum	100% (1/1)	
Corynebacterium simulans	100% (1/1)	
Corynebacterium sp. nov. 17	100% (1/1)	
Corynebacterium sp. nov. 18	100% (1/1)	
Enterococcus cloacae	100% (3/3)	
Enterococcus faecalis	100% (2/2)	
Kocuria rhizophila	100% (1/1)	
Microbacterium arborescens	100% (1/1)	

Microbacterium sp. nov. 10	100% (3/3)	
Staphylococcus lugdunensis	100% (1/1)	
Staphylococcus sciuri .	100% (1/1)	
Streptococcus oralis	100% (1/1)	
Streptococcus sanguis	100% (1/1)	
GRAM-NEGATIVE BACTERIA		
Chlamydia trachomatis	96% (23/24)	100% (20/20)
Acinetobacter baumannii	100% (1/1)	
Acinetobacter lwoffi	100% (5/5)	
Acinetobacter genosp. Nov. CC	100% (1/1)	
Acinetobacter genosp. Nov. Y	100% (1/1)	
Acinetobacter GENOSPECIES NOV.		100% (5/5)
Klebsiella pneumoniae	100% (3/3)	
Klebsiella oxytoca	100% (1/1)	
Acinetobacter junii	100% (4/4)	
Pantoea spp.	100% (3/3)	
Achromobacter xylosoxidans	100% (2/2)	
Aeromonas caviae	100% (1/1)	
Aeromonas hydrophilia	100% (1/1)	
Citrobavter koseri	100% (1/1)	
Citrobavter diversus	100% (1/1)	
Moraxella osloensis	100% (1/1)	
Morganella morganii	100% (2/2)	
Pseudomonas aeruginosa	100% (2/2)	
Chryseomonas luteola	100% (1/1)	
Enterobacteriaceae genus nov. 4	100% (1/1)	
Proteus mirabilis	100% (1/1)	
Pseudomonas oryzihabitans	100% (1/1)	
Ralstonia pickettii	100% (1/1)	
Ralstonia sp. nov. A	100% (1/1)	

Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline.

Reviewer's Comments:

The Division of Scientific Investigations (DSI) identified discrepancies between the microorganisms reported by the central microbiology laboratory and the applicant's database. This was reported for multiple investigation sites participating in protocols C-00-55, C-00-46, and C-01-34. Applicant's explanation of the discrepancies was that they reflected the differences between the preliminary identification of organisms by the central microbiology laboratory and the definitive identification by the applicant's own microbiology laboratory. It is the current policy of CDER that the applicant should not act as its own central laboratory. An independent central laboratory should confirm differences. For this submission, the agency considers the microorganisms identified by the central laboratory to be definitive. The microorganisms listed for the MOXFX treatment group in the above table includes only those organisms identified by the central laboratory.

Microbiological efficacy is demonstrated primarily against Chlamydia trachomatis, Staphylococcus aureus, Staphylococcus epidermidis, and Staphylococcus haemolyticus.

Study #1 **Protocol No. C-01-34** **Conducted 12/3/01 to 7/30/02**

Title: An Evaluation of the Safety and Clinical Improvement Rate of Ciprofloxacin Ophthalmic Solution 0.3% and Moxifloxacin Ophthalmic Solution 0.5% in Neonates with Presumed Bacterial Conjunctivitis

Study Design: A multi-center, randomized, double-blinded, active-controlled, parallel group study.

Test Drug Schedule: Patients received one drop of masked study medication in both eyes three times a day for four days.

Investigator Number	*Investigator*	Number Randomized	
		MOXFX	Ciloxan
3514	Wesley Alderete, M.D. Colleyville, TX 76034 USA	0	0
3495	Victoria Sanchez-Bal, M.D. Paramount, CA 90723 USA	9	10
3388	Barry T. Bloom, M.D. Wichita, KS 67214 USA	2	2
3530	A. Clifton Cage, D.O. Fort Worth, TX 76107 USA	1	0
3452	Ralph M. Conti, M.D. Henderson, NV 89014 USA	9	9
3427	Russell E. Delaney, M.D. Salt Lake City, UT 84121 USA	0	0
3510	R. Margarita Del Valle, M.D. Los Angeles, CA 90022 USA	0	0
1637	Diana DeSantis, M.D. Englewood, CO 80112 USA	2	2
3440	Mark S. Dorfman, M.D. Hollywood, FL 33020 USA	3	3
3433	Meyer Dworsky, M.D. Huntsville, AL 35801 USA	2	2
3460	John P. Frey, M.D. Monroe, WI 53566 USA	2	2
2910	Charlise A. Gunderson, M.D. Galveston, TX 77555 USA	0	0
3568	Jeffrey A. Hirschfield, M.D.	2	2

		Number Randomized	
	St. Petersburg, FL 33710 USA		
3475	**Ronald C. Jones, M.D.** Provo, UT 84604 USA	8	9
3455	**Michael H. Lauret. M.D.** Provo, UT 84604 USA	6	4
3535	**Michael L. Levin, M.D.** Henderson, NV 89014 USA	3	3
2508	**Stephen R. Luber. M.D.** Spokane, WA 99202 USA	4	3
3423	**Stephen T. Moffitt, M.D.** Trenton, NJ 08607 USA	2	1
3314	**Julee S. Morrow. M.D.** Fort Worth, TX 76104 USA	0	1
3489	**Corazon I. Oca. M.D.** Fountain Valley, CA 92708 USA	2	2
3517	**Steve I. Oshman. M.D.** Corpus Christi, TX 78411 USA	12	12
2475	**William D. Parker. M.D.** Shreveport, LA 71105 USA	3	3
3461	**Hamsa Ramkumar. M.D.** Whittier, CA 90603 USA	0	0
3474	**Raymond Rosenberg. M.D.** Stone Mountain, GA 30087 USA	0	0
3169	**Tommy J. Schechtman, M.D.** Palm Beach Gardens, FL 33410 USA	0	0
3482	**Robert Schelonka. M.D.** Birmingham, AL 35233 USA	2	1
2234	**Richard H. Schwartz. M.D.** Vienna, VA 22180 USA	2	2
3463	**Peter E. Silas. M.D.** Layton, UT 84041 USA	24	23

		Number Randomized	
3348	Rafael A. Solis, M.D. North Hollywood, CA 91605 USA	5	5
3437	Arthur A. Strauss, M.D. Long Beach, CA 90806 USA	0	0
3479	Jonathan M. Whitfield, M.D. Dallas, TX 75246 USA	0	0
3498	Lynette R. Wilson-Phillips, M.D. Clarkston, GA 30021 USA	2	1

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

Study Design

This was a multi-center, randomized, double-blinded, active-controlled, parallel group study designed to evaluate the safety and clinical improvement rate of moxifloxacin ophthalmic solution 0.5% (MOXFX) and ciprofloxacin ophthalmic solution o.3% (Ciloxan) in neonates from birth to one month of age with presumed bacterial conjunctivitis. A minimum of either 100 subjects culture positive for bacteria or 200 subjects with red eyes were to be enrolled.

Eligible who met all inclusion/exclusion criteria were randomized into one of two treatment groups, MOXFX or Ciloxan, one drop to both eyes three times a day. Treatment continued for four days with a test-of-cure follow-up at Day 9. The patients were evaluated at on Days 1 (Screening), 2, 3, 4, 5 (end-of-therapy), and 9 (test-of-cure). At each visit, vital signs and an ophthalmic exam consisting of pupil, red reflex, and anterior segment anatomy evaluations were performed. Ocular bacteriological cultures were performed on Day 1 and at the time a patient exited from the study. Investigators rated the ocular signs at every visit.

Study Medications

- Moxifloxacin ophthalmic solution, 0.5% (Lot # 00-500222-1 and 00-500380-1, Formulation Identification # 101149)
- Ciloxan ophthalmic solution 0.3% (Lot # 01-500295-1, Formulation Identification # 11255)

Inclusion Criteria

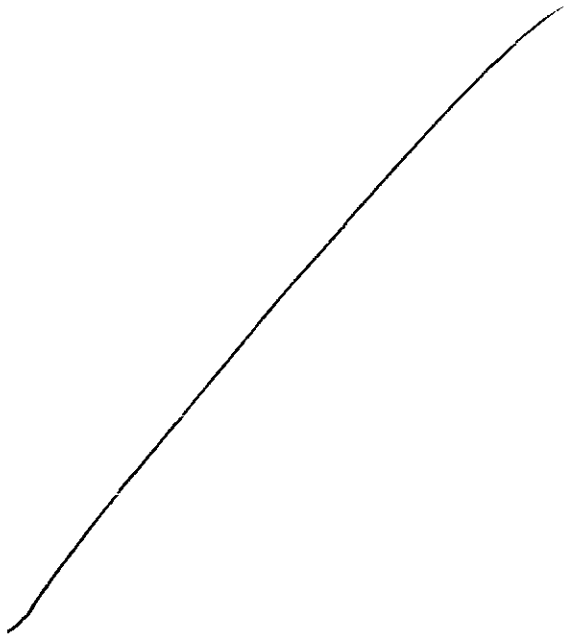
1. Children 0-1 month of age at screening (e.g., if date of birth is 2/17/02, subject may not be enrolled after 3/17/02), of either sex and of any race.

2. In-patients in a hospital neonatal intensive care unit or non-hospitalized children.
3. Have a clinical diagnosis of presumed bacterial conjunctivitis in at least one eye based on clinical observation including a rating of ≥ 1 bulbar conjunctival injection and/or ≥ 1 conjunctival discharge/exudate. If subject is eligible for the study based on discharge/exudate score, a conjunctival smear will be taken and evaluated for evidence of gonococcus.
4. Parent or legally acceptable representative has read, understood, and signed an informed consent form approved by an Institutional Review Board.

Exclusion Criteria

1. Children older than 1 month of age.
2. Suspected or confirmed ophthalmia neonatorum of gonococcal, chlamydia, herpetic, or chemical origin. If the conjunctival culture or smear taken at the Screening Visit demonstrate evidence of gonococcal ophthlmia neonatorum, the subject will be exited from the study and referred for appropriate treatment.
3. Children of birth mothers with any sexually transmitted disease (STD) within one month prior to delivery and/or a positive test for human immunodeficiency virus (HIV).
4. Suspected fungal, viral (e.g., Herpes simplex) or Acanthamoeba infection in either eye.
5. Use of any concomitant topical ocular medications during the course of the study or within 48 hours of the Screening Visit (Day 1).
6. Use of an oral, intravenous, or ocular antibacterial within 96 hours of the Screening Visit (Day 1) or during the study.
7. Known or suspected allergy or hypersensitivity to fluoroquinolones or to any components of the study medications.
8. Any systemic or ocular pathology that, in the opinion of the investigator, would negatively affect the conduct or outcome of the study, or impact the safety of the child.
9. Any current immunosuppressive disorder (e.g., HIV-positive), or use of immunosuppressive therapy.
10. Therapy with another investigational agent prior to the study or concurrent with this study.
11. Abnormal pupillary reflex in either eye.
12. Any abnormality in the posterior segment of either eye or visual axis as determined by the red reflex test.
13. Abnormal ocular anterior segment anatomy in either eye.
14. Infants being treated for retinopathy of prematurity or at risks for eye problems such as those with family histories of congenital cataracts, retinoblastoma or other relevant genetic disorders.

Additionally, the Alcon Medical Monitor may declare any subject ineligible for a valid medical reason.



Safety Variables

The safety variables were adverse events, ocular exam, and vital signs (body temperature, respiration rate, blood pressure, and pulse).

Study Plan

Parameters	Day 1 Screening	Day 2	Day 3	Day 4	Day 5 End-of Therapy	Day 9 Test-of-Cure[f]	Early Termination[b]
Screen Patients	X						
Informed Consent	X						
Demographics	X						
Medical History	X						
Concomitant meds/general health	X	X	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X	X	X
Collect Ocular Culture	X					X	X
Conjunctival Smear[d]	X						
Ocular Signs[e]	X	X	X	X	X	X	X
Assess pupils, red reflex, and anterior segment anatomy[g]	X		X	X	X	X	X
Dispense Study Medication	X						
Dose Study Medication (in office)[h]	X[i]						
Adverse Event Reporting	X[a]	X	X	X	X	X	X

Collect Study Medication					X		X
Exit Patients						X	X
Schedule ophthalmologist exam within 24 hours							X

[a] After first dose. [b] Test patients discontinued prior to study Day 9 (Test-of-Cure), including treatment failures. An ophthalmologist must examine the patient within 24 hours of the exit visit. [c] To include blood pressure (systolic and disatolic), respiration rate, pulse rate, and body temperature. [d] Smear taken when patient has a conjunctival exudate/discharge score ≥ 1 at Day 1 (Screening) or at subsequent visits if prior scores are zero. [e] Penlight or ophthalmoscope may be used. [f] Day 9 exam to be conducted by an ophthalmologist. [g] Penlight may be use for pupils and anterior segment anatomy. Ophthalmoscope required for red reflex assessment. [h] Non-hospitalized patients. [i] Initial dose only.

Subject Disposition and Demographics

All 209 randomized subjects received treatment and 201 subjects completed the study.

Subject Disposition

	Number of Subjects		
	MOXFX N (%)	Ciloxan N (%)	Total N (%)
Randomized	107	102	209
Discontinued prematurely	8 (7.5)	0 (0.0)	8 (3.8)
Included in safety evaluations	107 (100.0)	102 (100.0)	209 (100.0)
Included in intent-to-treat efficacy analysis	107 (100.0)	102 (100.0)	209 (100.0)
Included in modified per protocol efficacy analysis	67 (62.6)	70 (68.6)	137 (65.6)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Reason
2475	304	MOXFX	Treatment failure
3388	604	MOXFX	Treatment failure
3423	902	MOXFX	Treatment failure
3452	648	MOXFX	Treatment failure
3482	2202	MOXFX	Per investigator, ocular assessment on Day 5
3495	276	MOXFX	Patient decision
3517	2109	MOXFX	Patient decision
	9152	MOXFX	Noncompliance

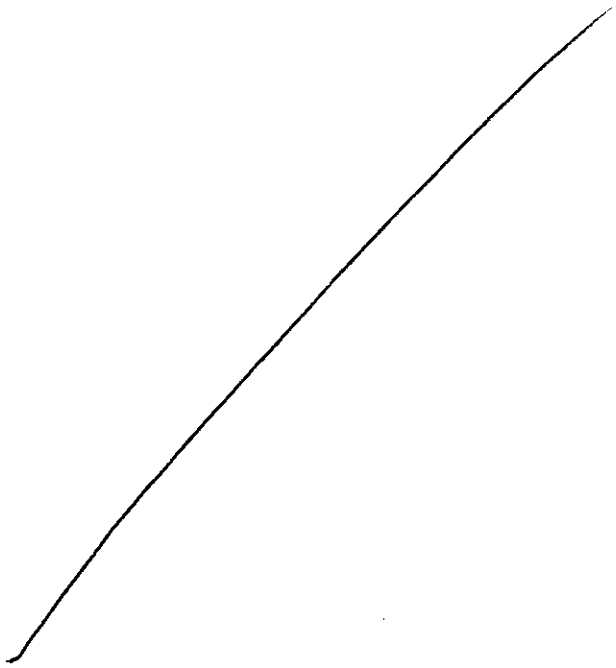
Summary of Demographics

	Modified Per Protocol			Intent-to-Treat		
	MOXFX	Ciloxan	P-value[a]	MOXFX	Ciloxan	P-value[a]
Number of Patients:	67	70		107	102	
AGE (days)			0.4696			0.9740
MEAN(SD)	16.2(6.6)	17.0(5.9)		16.4(6.8)	16.4(6.1)	
MIN-MAX	5-30	7-29		3-30	2-29	
0-27 days	63 (94.0)	66 (94.3)	1.0000	100 (93.5)	97 (95.1)	0.6104
28 days-23 months	4 (6.0)	4 (5.7)		7 (6.5)[b]	5 (4.9)[b]	
SEX: N (%)			0.0736			0.1857
Female	38 (56.7)	29 (41.4)		57 (53.3)	45(44.1)	
Male	29 (43.3)	41 (58.6)		50 (46.7)	57(55.9)	

RACE: N (%)			0.4406			0.5116
Caucasian	47 (70.1)	45 (64.3)		78 (72.9)	70 (68.6)	
Black	2 (3.0)	1 (1.4)		3 (2.8)	3 (2.9)	
Asian	2 (3.0)	0 (0.0)		2 (1.9)	0 (0.0)	
Other	16 (23.9)	24 (34.3)		24(22.4)	29 (28.4)	

[a] P-value for age based on analysis of variance. P-values for age range, sex, and race based on Chi-square test of independence (or Fishers Exact test if N<5). [b] All 12 patients in the 28 days – 23 months age group were < 31 days old.

Efficacy



NDA 21-598 and ——— moxifloxacin hydrochloride ophthalmic solution 0.5%

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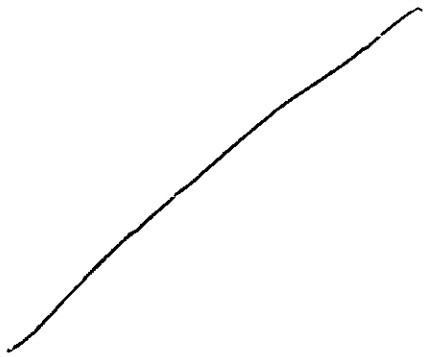
✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



6.4 The submitted studies in NDA 21-598 are sufficient to establish efficacy for the use of MOXFX in the treatment of bacterial conjunctivitis in patients older than 1 year of age. The clinical cure rate for susceptible microorganisms is approximately 70%.

7 Integrated Review of Safety

7.1 The submitted studies in NDA 21-598 and [redacted] demonstrate an acceptable safety profile with the use of MOXFX for the treatment of bacterial conjunctivitis. The most frequently reported adverse event with is ocular discomfort (1-6%).

7.2 The safety database consists of safety data from three clinical trials, Protocols C-00-55, C-00-46, and C-01-34.

7.3 The safety database consists of 1307 subjects from three clinical trials (Protocols C-00-55, C-00-46, and C-01-34) with presumed bacterial conjunctivitis. The number of patients exposed to MOXFX was 654, 274

for vehicle, 277 for OCUFX, and 102 for Ciloxan. The dosing regimen for MOXFX was 1 drop to both eyes TID for 4 days.

7.4 Study #1 Protocol C-00-55

Safety

Adverse Events

All 544 subjects who enrolled in the study received treatment and were included in the safety analysis. No deaths occurred during the study. One subject (#3522) in the Vehicle treatment group experienced two serious adverse events (asthenia, hypokalemia) and discontinued from the study due to hypokalemia. Five subjects (1.9%) receiving MOXFX and eight subjects (2.9%) receiving Vehicle prematurely discontinued from the study due to adverse events.

Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	MOXFX (N=270)	Vehicle (N=274)
	N (%)	N (%)
OCULAR		
Discomfort eye	15 (5.6)	6 (2.2)
Conjunctivitis	5(1.9)	4 (1.5)
Hemorrhage subconjunctival	4 (1.5)	3 (1.1)
Dry eye	3 (1.1)	3 (1.1)
Keratitis	3 (1.1)	3 (1.1)
Pain eye	3 (1.1)	3 (1.1)
Pruritus eye	3 (1.1)	
Visual acuity decrease	3 (1.1)	3 (1.1)
Infiltrate corneal		4 (1.5)
NON-OCULAR		
Body as a whole		
Infection	10 (3.7)	9 (3.3)
Fever	5 (1.9)	
Injury accidental	4 (1.5)	
Headache	3 (1.1)	6 (2.2)
Digestive System		
Vomiting		6 (2.2)
Respiratory System		
Cough increase	5 (1.9)	8 (2.9)
Pharyngitis	4 (1.5)	7 (2.6)
Rhinitis	4 (1.5)	5 (1.8)
Skin and Appendages		
Dermatitis		3 (1.1)
Herpes simplex		3 (1.1)
Special Senses		
Otitis media	6 (2.2)	4 (1.5)

Visual Acuity

Change in logMAR Visual Acuity from Baseline to Final Visit

Line Changes	MOXFX (N=270)	Vehicle (N=274)
N (%)	185 (96.5)	184 (67.2)
≥ 2 lines loss	6 (3.2)	16 (8.7)
1 line loss	23 (12.4)	18 (9.8)
No Change	120 (64.9)	117 (63.6)
1 line gain	25 (13.5)	21 (11.4)
≥ 2 lines gain	10 (5.4)	9 (4.9)

Ocular Signs

Clinically Relevant Changes* in Ocular Signs Parameters
– Baseline to Final Visit

Treatment	Total	Changes in Ocular Signs Parameters	
	N (%)	Cornea N (%)	Iris/Anterior Chamber N (%)
Total	537 (100.0)	3 (0.6)	1 (0.2)
MOXFX	270 (50.3)	0 (0.0)	0 (0.0)
Vehicle	271 (50.5)	3 (1.1)	1 (0.4)

* Clinically relevant changes were defined as any increase ≥ 1 units from baseline.

Fundus Exam

No patient experienced a clinically relevant change (an increase of one or more units from baseline) in fundus parameters from baseline to exit.

Study #2 Protocol No. C-00-46

Safety

Adverse Events

All 554 subjects who enrolled in the study received treatment and were included in the safety analysis. No deaths occurred during the study. Two subjects (0.7%) in the OCUFX treatment group experienced a serious adverse event. Two subjects (0.7%) receiving OCUFX and none of the subjects receiving MOXFX prematurely discontinued from the study due to an adverse event.

Serious Adverse Events

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
3059	9107	OCUFX	Dacryocystitis	Resolved w/Tx	Yes
3051	2006	OCUFX	Arrhythmia	Resolved w/Tx	No

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates Greater than 1%

Coded	MOXFX	OCUFX

Adverse Event	(N=277)	(N=277)
	N (%)	N (%)
OCULAR		
Keratitis	3 (1.1)	3 (1.1)
Discomfort eye	4 (1.4)	
Infiltrate corneal		3 (1.1)

Visual Acuity

Change in logMAR Visual Acuity from Baseline to Final Visit

Line Changes	MOXFX (N=277)	OCUFX (N=277)
N (%)	267 (96.4)	269 (97.1)
≥ 2 lines loss	1 (0.4)	0 (0.0)
1 line loss	1 (0.4)	2 (0.7)
No Change	263 (98.5)	264 (98.1)
1 line gain	2 (0.7)	2 (0.7)
≥ 2 lines gain	0 (0.0)	1 (0.4)

p-value=0.7360 – Cochran-Mantel-Haenszel rank scores test

Ocular Signs

Clinically Relevant Changes* in Ocular Signs Parameters

Treatment	Total	Changes in Ocular Signs Parameters	
	N (%)	Cornea N (%)	Iris/Anterior Chamber N (%)
Total	554 (100.0)	12 (2.2)	1 (0.2)
MOXFX	277 (50.3)	4 (0.0)	0 (0.0)
OCUFX	277 (50.5)	8 (1.4)	1 (0.4)

* Clinically relevant changes were defined as any increase ≥ 1 units from baseline.

Fundus Exam

No patients experienced a clinically relevant increase (≥ one unit increase from baseline) in fundus parameters.

Study #3 Protocol No. C-01-34

All 209 subjects who enrolled in the study received treatment and were included in the safety analysis. No deaths occurred during the study. Two subjects (1.9%) in the MOXFX treatment group experienced a serious adverse event. No subjects discontinued from the study due to an adverse event.

Serious Adverse Events

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
3452	637	MOXFX	Pyloric stenosis	Resolved w/Tx	No
3463	251	MOXFX	Fever	Resolved w/Tx	No

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates 1% and Greater

Coded Adverse Event	MOXFX (N=107)	Ciloxan (N=102)
	N (%)	N (%)
OCULAR		
Tearing	3 (2.8)	2 (2.0)
Hyperemia eye	2 (1.9)	1 (1.0)
Edema lid		1 (1.0)
Hemorrhage eye		1 (1.0)
NON-OCULAR		
Body as a Whole		
Surgical/Medical procedure	2 (1.9)	3 (2.9)
Fever		2 (2.0)
Infection		2 (2.0)
Digestive System		
Monilia oral		3 (2.9)
Vomiting		3 (2.9)
Eructation	2 (1.9)	
Nervous System		
Irritability		1 (1.0)
Respiratory System		
Rhinitis	2 (1.9)	4 (3.9)
Bronchitis		1 (1.0)
Skin and Appendages		
Rash	3 (2.8)	3 (2.9)
Special Senses		
Otitis media		1 (1.0)

Ocular Signs

No clinically relevant changes (any change from normal to abnormal) in ocular exam parameters (pupils, red reflex, anterior segment) were reported for any patient in the study.

Cardiovascular

Mean Change from Baseline to Exit for Cardiovascular Parameters

	Newborn (0 to 27 days)	Neonates (28 days to 31 days[a])	Overall Safety Population (all ages)
Parameter	Mean Change (N)	Mean Change (N)	Mean Change (N)
Pulse (bpm)			
MOXFX	-0.3 (98)	-9.2 (5)	-0.8 (103)
Ciloxan	-0.3 (93)	-3.8 (5)	-0.5 (98)
Treatment Group Comparison	NS	NS	NS
Systolic Blood Pressure (mmHg)			
MOXFX	2.4 (75)	-7.5 (4)	1.9 (79)
Ciloxan	-0.1 (70)	2.2 (5)	0.0 (75)

Treatment Group Comparison	NS	NS	NS
Diastolic Blood Pressure (mmHg)			
MOXFX	2.1* (70)	-4.5 (4)	1.7 (74)
Ciloxan	-0.4 (68)	-4.0 (5)	-0.6 (73)
Treatment Group Comparison	SS	SS	SS

[a] All patients in the 28 days to 31 days age group were < 31 days old. * = statistically significant ($p<0.05$) based upon change from baseline to exit. NS = not statistically significant ($p>0.05$) SS = statistically significant ($p<0.05$)

No clinically relevant change (any change from normal to abnormal) between treatment groups were observed for cardiovascular parameters.

7.5 There is no pharmacologic evidence for any potential for drug abuse with MOXFX.

7.6 The safety database from the three submitted clinical studies in —— and NDA 21-598 is adequate.

7.7 There are no labeling safety issues.

8 Dosing, Regimen, and Administration Issues

The proposed dosing regimen is supported by data from Study C-00-02.

9 Use in Special Populations

9.1 Applicant's analyses on the effects of gender, age, race, and ethnicity on efficacy and safety are adequate.

9.2 In response to the agency's pediatric written request, the applicant conducted Study C-01-34, ——

9.3 No additional data in other special populations are needed.

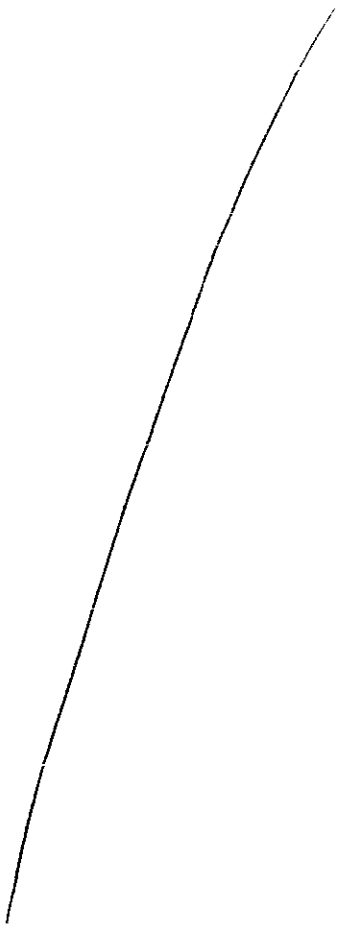
10 Conclusions, Recommendations, and Labeling

10.1 The submitted studies in NDA 21-598 are sufficient to establish efficacy for the use of MOXFX in the treatment of bacterial conjunctivitis in susceptible microorganisms in patients older than 1 year of age.

The submitted studies in NDA 21-598 and ——— demonstrate an acceptable safety profile with the use of MOXFX for the treatment of bacterial conjunctivitis. The most frequently reported adverse event is ocular discomfort.

10.2 NDA 21-598 is recommended for approval for the treatment of bacterial conjunctivitis in susceptible microorganisms in patients older than 1 year of age.

10.3 *Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.*



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

_____ § 552(b)(5) Deliberative Process

___✓___ § 552(b)(5) Draft Labeling

Appendix

1 Summary of Adverse Events

Summary of Frequency and Incidence of Ocular and Non-Ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	MOXFX		
Protocol	C-00-55 N=270	C-00-46 N=277	C-01-34 N=107
	N (%)	N (%)	N (%)
OCULAR			
Discomfort eye	15 (5.6)	4 (1.4)	
Conjunctivits	5 (1.9)		
Hemorrhage subconjunctival	4 (1.5)		
Dry eye	3 (1.1)		
Keratitis	3 (1.1)	3 (1.1)	
Pain eye	3 (1.1)		
Pruritus eye	3 (1.1)		
Visual acuity decrease	3 (1.1)		
Tearing			3 (2.8)
Hyperemia eye			2 (1.9)
NON-OCULAR			
Body as a Whole			
Infection	10 (3.7)		
Fever	5 (1.9)		
Injury accidental	4 (1.5)		
Headache	3 (1.1)		
Surgical/Medical procedure			2 (1.9)
Digestive System			
Eructatation			2 (1.9)
Respiratory System			
Cough increase	5 (1.9)		
Pharyngitis	4 (1.5)		
Rhinitis	4 (1.5)		2 (1.9)
Skin and Appendages			
Rash			3 (2.8)
Special Senses			
Otitis media	6 (2.2)		

2 Summary of Protocol C-00-02

Protocol C-00-02 was a multi-center, double-blinded, vehicle, randomized, parallel group study comparing moxifloxacin ophthalmic solution 0.5% (MOXFX) to moxifloxacin vehicle (Vehicle) (1:1:1:1) in patients at least one year of age with suspected bacterial conjunctivitis. The patients were randomized to one of four treatment groups, MOXFX one drop two times a day for 3 days, MOXFX two drops two times a day for 3 days, Vehicle one drop two times a day for 3 days, and Vehicle two drops two times a day for 3 days. Targeted enrollment was 35 patients per arm.

Study Plan

Parameter	Day 1 (Screening) Exam	Day 2 Exam	Day 3 Exam	Day 4 (End-of-Therapy) Exam	Day 7 (Test-of-Cure) Exam
General Information; Medical History	X				
Informed Consent	X				
Pregnancy Test, When Applicable[a]	X				X
Visual Acuity	X				X
Collect Ocular Culture[b]	X			X	X
Slit-lamp Exam	X	X	X	X	X
Fundus Exam	X				X
Dispense Study Medication	X	X	X		
Dose Study Medication	X				
Collect Study Medication		X	X	X	
Record Adverse Events	X	X	X	X	X
Complete Exit Form[c]					X

[a]Was done before instillation of drug and at any time a patient discontinued from the study, or at the completion of the trial.
[b]At Day 1, Day 4, Day 7 and on all treatment failures.
[c]At any time a patient discontinued from the study, or at the completion of the trial on Day 7.

The primary clinical efficacy variable was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection (the sum of bulbar conjunctival injection and conjunctival discharge/exudate scores equals zero) at the test-of-cure (day 7) visit. The primary microbiological efficacy variable was the eradication rate of ocular pathogens at the test-of-cure visit.

Summary of Clinical Cure and Microbial Eradication by Study Day

Study Day **Modified Intent-to-Treat (MITT)**	Outcome	MOXFX 2 drops BID	Vehicle 2 drops BID	P-value[a]	MOXFX 1 drop BID	Vehicle 1 drop BID	P-value[a]
Day 4 (end-of-therapy)	Clinical cure	63% (17/27)	46% (22/46)	0.1541	65% (17/26)	46% (22/48)	0.1078
Day 7 (test-of-cure)	**Clinical cure**	**70% (19/27)**	**51% (26/51)**	**0.0991**	**78% (21/27)**	**51% (26/51)**	**0.0214**
	Microbial eradication	**85% (22/26)**	**50% (25/50)**	**0.0032**	**78% (21/27)**	**50% (25/50)**	**0.0177**
Study Day **Intent-to-Treat (ITT[b])**	Outcome						
Day 4 (end-of-therapy)	Clinical cure	54% (19/35)	45% (30/66)	0.3981	62% (24/39)	45% (30/66)	0.1111
Day 7 (test-of-cure)	**Clinical cure**	**71% (25/35)**	**52% (34/66)**	**0.0533**	**62% (31/39)**	**52% (34/66)**	**0.0043**

[a]Chi-square test of independence (or Fishers Exact test if N<50)
[b]ITT=All patients who received treatment and had at least one on-therapy visit. Patients who had no measurements after baseline were included as treatment failures.
[c]MITT= All patients who received treatment, had at least one on-therapy visit, met inclusion/exclusion criteria, and were culture positive for bacteria on Day 1. Patients who had no measurements after baseline were included as treatment failures.

The safety data is comparable to the safety data from protocols C-00-55 and C-00-46.

Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates 1% and Greater

Coded Adverse Event	MOXFX 1 drop (N=39)	MOXFX 2 drops (N=35)	Vehicle 1 drop (N=34)	Vehicle 2 drops (N=32)
	N (%)	N (%)	(N%)	(N%)
OCULAR				
Dry eye	1 (2.6)			
Hemorrhage subconjunctival	1 (2.6)			
Injury accidental	1 (2.6)			
Pain eye	1 (2.6)			
Pruritus eye		2 (5.7)		
Discomfort eye		1 (2.9)		
Eye disorder		1 (2.9)		
Irritation eye				1 (3.1)
NON-OCULAR				
Body as a Whole				
Infection	2 (5.1)	3 (8.6)		2 (6.3)
Flu syndrome	1 (2.6)			
Headache		1 (2.9)	3 (8.8)	
Cold syndrome		1 (2.9)		
Fever		1 (2.9)		
Allergy			2 (5.9)	1 (3.1)
Injury accidental				1 (3.1)
Digestive System				
Vomit		1 (2.9)		1 (3.1)
Diarrhea		1 (2.9)		
Hemolytic and Lymphatic				
Lymphadenopathy			1 (2.9)	

Microbial Eradication Rates from Baseline to Final by Organism

Organism	MOXFX	Vehicle
GRAM-POSITIVE BACTERIA		
Staphylococcus epidermidis	100% (10/10)	67% (2/3)
Streptococcus pneumoniae	60% (3/5)	50% (3/6)
Staphylococcus aureus	100% (7/7)	
Staphylococcus warneri	100% (1/1)	
Microbacterium otitidis	71% (12/17)	53% (8/13)
Microbacterium "harmaniae"	100% (1/1)	60% (2/3)
GRAM-NEGATIVE BACTERIA		
Haemophilus influenzae	89% (8/9)	67% (6/9)
Haemophilus *"alconae"*	100% (4/4)	75% (6/8)
Haemophilus sp. nov. 2		100% (1/1)
Acinetobacter genospecies 3	100% (1/1)	
Pseudomonas aeruginosa	100% (1/1)	
Serratia marcescens	100% (1/1)	
Enterobacter aerogenes		100% (1/1)

Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline.

3 Summary of Microbial Eradication Rates

Summary of Microbial Eradication Rates by Final Organism
Protocol Nos. C-00-02, C-00-55, C-00-46, and C-01-34

Organism	MOXFX	OCUFX	Ciloxan	Vehicle
GRAM-POSITIVE BACTERIA				
Staphylococcus epidermidis	98% (82/84)	98% (43/44)	97% (32/33)	86% (19/22)
Staphylococcus aureus	100% (48/48)	100% (13/13)	100% (3/3)	56% (5/9)
Staphylococcus haemolyticus	95% (18/19)	100% (10/10)		
Staphylococcus hominis	100% (12/12)	56% (5/9)	100% (1/1)	
Staphylococcus capitis	100% (4/4)		100% (1/1)	
Staphylococcus warneri	100% (5/5)			
Staphylococcus intermedius	100% (1/1)			
Staphylococcus lugdunensis	100% (1/1)		100% (1/1)	
Staphylococcus saprophyticus	100% (1/1)	100% (5/5)		
Staphylococcus sciuri	100% (1/1)			
Staphylococcus simulans	100% (1/1)			
Streptococcus pneumoniae	80% (24/30)		100% (3/3)	61% (20/33)
Streptococcus "schlechii"	100% (2/2)			
Streptococcus mitis	100% (4/4)		100% (4/4)	
Streptococcus pyogenes	100% (2/2)			
Streptococcus salivarius	100% (2/2)			
Streptococcus oralis	100% (1/1)			
Streptococcus sanguis	100% (1/1)			
Streptococcus sanguis subsp. nov.	100% (1/1)			
Streptococcus parasanguinis subsp. A	100% (1/1)			
Streptococcus sp. nov. 6	100% (1/1)			
Streptococcus viridans group sp. nov. F	100% (1/1)			
Streptococcus viridans group sp. nov. J	100% (1/1)			
Streptococcus viridans group sp. nov. M	100% (1/1)			
Streptococcus viridans group sp. nov. W	100% (1/1)			
Other viridans Streptococcus			100% (3/3)	
Corynebacterium amycolatum	100% (2/2)			
Corynebacterium argentoratense	100% (1/1)			
Corynebacterium simulans	100% (1/1)			
Corynebacterium sp. nov. 17	100% (1/1)			
Corynebacterium sp. nov. 18	100% (1/1)			
Enterococcus cloacae	100% (3/3)			
Enterococcus faecalis	100% (2/2)			
Micrococcus luteus	100% (6/6)			
Kocuria rhizophilia	100% (1/1)			
Kocuria Kristinae	100% (1/1)			
Microbacterium arborescens	100% (1/1)			
Microbacterium sp. nov. 10	100% (3/3)			
Microbacterium otitidis	100% (1/1)			53% (8/13)
Microbacterium "harmaniae"	100% (1/1)			60% (2/3)
Bacillus sp. nov. 3	100% (1/1)			
GRAM-NEGATIVE BACTERIA				
Chlamydia trachomatis	96% (23/24)	100% (20/20)		
Haemophilus influenzae	80%(31/39)			67% (6/9)
Haemophilus parainfluenzae	100% (6/6)			
Haemophilus sp. nov. *"alconae"*			100% (1/1)	75% (6/8)

Acinetobacter GENOSPECIES NOV.		100% (5/5)		
Acinetobacter junii	100% (4/4)			
Acinetobacter baumanii	100% (2/2)			
Acinetobacter lwoffi	100% (5/5)			
Acinetobacter genosp. nov. CC	100% (1/1)			
Acinetobacter genosp. nov. Y	100% (1/1)			
Acinetobacter genospecies 3	100% (1/1)			
Acinetobacter johnsonii			100% (1/1)	
Klebsiella pneumoniae	100% (4/4)			
Klebsiella oxytoca	100% (1/1)		100% (1/1)	
Pantoea sp.	100% (3/3)			
Moraxella catarrhalis	100% (1/1)		100% (3/3)	
Moraxella osloensis	100% (1/1)			
Pseudomonas aeruginosa	100% (4/4)			
Pseudomonas oryzihabitans	100% (1/1)			
Enterobacter aerogenes			100% (1/1)	
Enterobacteriaceae genus nov. 4	100% (1/1)			
Escherichia coli			100% (1/1)	
Achromobacter xylosoxidans	100% (2/2)			
Aeromonas caviae	100% (1/1)			
Aeromonas hydrophilia	100% (1/1)			
Citrobavter koseri	100% (2/2)			
Citrobavter diversus	100% (1/1)			
Morganella morganii	100% (2/2)			
Chryseomonas luteloa	100% (1/1)			
Proteus mirabilis	100% (1/1)			
Serratia marcescens	100% (1/1)			
Leclercia adecarboxylata	100% (1/1)			
Stenotrophomonas maltophila			100% (1/1)	
Ralstonia pickettii	100% (1/1)			
Ralstonia sp. nov. A	100% (1/1)			

Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline.

Reviewer's Comments:

The Division of Scientific Investigations (DSI) identified discrepancies between the microorganisms reported by the central microbiology laboratory and the applicant's database. This was reported for multiple investigation sites participating in protocols C-00-55, C-00-46, and C-01-34. Applicant's explanation of the discrepancies was that they reflected the differences between the preliminary identification of organisms by the central microbiology laboratory and the definitive identification by the applicant's own microbiology laboratory. It is the current policy of CDER that the applicant should not act as its own central laboratory. An independent central laboratory should confirm differences. For this submission, the agency considers the microorganisms identified by the central laboratory to be definitive. The microorganisms listed for the MOXFX treatment group in the above table includes only those organisms identified by the central laboratory.

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

NDA 21-598 and [redacted]
HFD-550/Div Files
HFD-550/MO/Lim
HFD-550/BIOPHARM/Zhang
HFD-550/CHEM/Tso
HFD-550/MICRO/Dionne
HFD-550/PHARM/Dou
HFD-550/PM/puglisi
HFD-550/Dep Div Dir/Chambers
HFD-550/Div Dir/Simon

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/s/

Lucious Lim
4/14/03 11:45:01 AM
MEDICAL OFFICER

Wiley Chambers
4/15/03 06:01:04 PM
MEDICAL OFFICER

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ON ORIGINAL

Medical Officer's Review of ——— and NDA 21-598

———

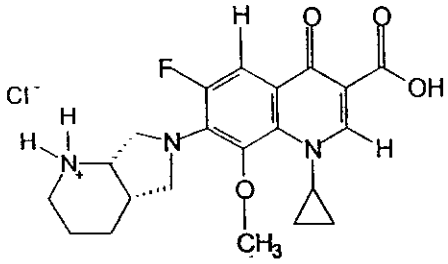
NDA 21-598
Medical Officer's Review #2

Submission Date: April 15, 2003
Review Completed: April 15, 2003

Proposed Trademark: Vigamox

Generic Name: Moxifloxacin hydrochloride ophthalmic Solution, 0.5%

Chemical Name:



$C_{21}H_{24}FN_3O_4 \bullet HCl$ Mol Wt 437.9

Sponsor:

Alcon, Inc.
P.O. Box 62
Bosch 69
CH-6331 Hunenberg
Switzerland

Authorized U.S. Agent
Alcon Research, Ltd.
6201 S. Freeway
Fort Worth, Texas
(817) 551-4933
Contact: Angela Kothe

Pharmacologic Category: Anti-infective (fluoroquinolone)

Submitted Submitted is applicant's proposed revised package insert.

✓ Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

7 § 552(b)(5) Draft Labeling

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Lucious Lim
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Wiley Chambers
4/15/03 07:26:36 PM
MEDICAL OFFICER

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Medical Officer's Review of ——— and NDA 21-598
120-Day Safety Update

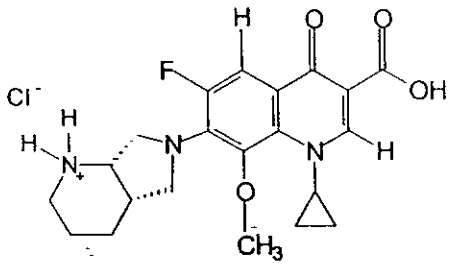
NDA ———
NDA 21-598
Medical Officer's Review

Submission Date: February 12, 2003
Review Completed: March 04, 2003

Proposed Trademark: To be determined

Generic Name: Moxifloxacin hydrochloride ophthalmic Solution, 0.5%

Chemical Name:



$C_{21}H_{24}FN_3O_4 \bullet HCl$ Mol Wt 437.9

Sponsor:

Alcon, Inc.
P.O. Box 62
Bosch 69
CH-6331 Hunenberg
Switzerland

Authorized U.S. Agent
Alcon Research, Ltd.
6201 S. Freeway
Fort Worth, Texas
(817) 551-4933
Contact: Angela Kothe

Pharmacologic Category: Anti-infective (fluoroquinolone)

Proposed Indication: Bacterial conjunctivitis

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

Submitted: 120-Day Safety Information for Protocols C-02-22, C-01-66, and C-02-19.

Summary of Safety Data

This Four-Month Safety Update includes new safety data from one completed study (C-02-22) and two ongoing studies (C-01-66 and C-02-19) since the filing of [redacted] NDA 21-598.

The completed study was a Phase 1, twelve (12) subject plasma pharmacokinetic study in healthy adult Japanese males [redacted] This study employed an exaggerated dosing regimen of one drop eight-times-daily in anticipation of initiating a [redacted] The database from this study has been locked and the data are unmasked.

Summary of Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates Greater than 1%

Adverse Event	MOXFX			
Study Completion Date	Pre NDA Filing			Post NDA Filing
Protocol	C-00-55 Study 1 (N=270)	C-00-46 Study 2 (N=277)	C-01-34 Study 3 (N=107)	C-02-22 Study 4 (N=8)
	N (%)	N (%)	N (%)	N (%)
OCULAR				
Discomfort eye	15 (5.6)	4 (1.4)		
Conjunctivitis	5 (1.9)			
Hemorrhage subconjunctival	4 (1.5)			
Dry eye	3 (1.1)			
Keratitis	3 (1.1)	3 (1.10		
Pain eye	3 (1.1)			
Pruritus eye	3 (1.1)			
Visual acuity decrease	3 (1.1)			
Tearing			3 (2.8)	
Hyperemia eye			2 (1.9)	
NON-OCULAR				
Body as a Whole				
Infection	10 (3.7)			
Fever	5 (1.9)			
Injury accidental	4 (1.5)			
Headache	3 (1.1)			2 (25.0)
Surgical/Medical procedure			2 (1.9)	
Cardiovascular System				
Hypertension				1 (12.5)
Digestive System				
Eructation			2 (1.9)	

Nausea				1 (12.5)
Vomit				1 (12.5)
GGTP increase				1 (12.5)
Metabolic and Nutrition				
SGPT increase (ALT)				5 (62.5)
Hyperlipidemia				2 (25.0)
SGOT increase (AST)				3 (37.5)
Respiratory System				
Cough increase	5 (1.9)			
Pharyngitis	4 (1.5)			
Rhinitis	4 (1.5)		2 (1.9)	1 (12.5)
Skin and Appendages				
Rash			3 (2.8)	
Special Senses				
Otitis media	6 (2.2)			

Reviewer's Comments:

Study C-02-22 contributed a total of 8 additional patients to the overall number of patients exposed to moxifloxacin ophthalmic solution (MOXFX). Except for the unusually high incidence of liver function tests (LFT) abnormalities, the safety data submitted with this update is comparable to the data reported in the original NDA. All subjects with abnormal LFT values at exit returned to baseline or within normal limits within a three-week period.

The ongoing studies include a randomized, double-masked, vehicle-controlled safety and efficacy study (C-01-66) and a randomized open-label pharmacokinetic study (C-02-19). Masked adverse event data for study C-01-66 were included in this update. No adverse events have been reported for study C-02-19.

Reviewer's Recommendation:

Safety data from studies C-01-66 and C-02-19 should be submitted to the agency when they become available.

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

NDA 21-598 and [redacted]
HFD-550/Div Files
HFD-550/MO/Lim
HFD-550/BIOPHARM/Zhang

HFD-550/CHEM/Tso
HFD-550/PHARM/Dou
HFD-550/PM/puglisi
HFD-550/Dep Div Dir/Chambers

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/s/

Lucious Lim
4/11/03 03:47:56 PM
MEDICAL OFFICER

Wiley Chambers
4/12/03 11:41:55 PM
MEDICAL OFFICER

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ON ORIGINAL

NDA 21-598

Labeling Review of [redacted] and NDA 21-598

Original Carton and Container Submission

Submission Date: 4/11/03
Receipt Date: 4/14/03
Review Date: 4/14/03

Applicant: Alcon Research, Inc.
6201 South Freeway
Fort Worth, Texas 76134

Applicant's Representative: Angela C. Kothe, OD, Ph.D.
Assistant Director, Regulatory Affairs
817-551-4933 Phone
817-551-4630 Fax

Drug: Vigamox™ (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Pharmacologic Category: Anti-infective

Submitted: Draft Carton and container labels for [redacted] NDA 21-598

Recommendations: *The draft carton and container labels may be approved provided the applicant agrees to the following:*

1. *The size of the container label for the 3 mL commercial product a [redacted] must be increased to more appropriately fit the 6 mL container. The 6 mL container can accommodate a larger container label.*
2. *The prominence of the font of the proprietary name and established name on the container and carton should be revised to more closely approximate each other an the established name should be at least half as large as the letters comprising the proprietary name.*
3. *The font size of all text on the container label for the 3 mL commercial product [redacted] must be increased to more appropriately fit a 6 mL container.*

Lisa M. Hubbard, R.Ph.

Wiley Chambers, M.D.

cc:

[redacted]

NDA 21-598
HFD-550/Clin Rev/Hubbard
HFD-550/MO/Lim
HFD-550/Dep Dir/Chambers
HFD-550/PM/Puglisi

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/s/

Lisa Hubbard
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Wiley Chambers
4/15/03 07:29:29 PM
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