CLINICAL REVIEW

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

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

1.2 Risk Benefit Assessment

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

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

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarket clinical study requirements and commitments.

2 Introduction and Regulatory Background

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

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

2.1 Product Information

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

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

2.2 Tables of Currently Available Treatments for Proposed Indications

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

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

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

2.6 Other Relevant Background Information

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

Moxifloxacin AF is not marketed in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

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

Investigators with financial Interests or Arrangements

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

Reviewer's Comments:

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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

Composition of Moxifloxacin AF Ophthalmic Solution

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

Comparison of Compositions of Moxifloxacin AF and Vigamox

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

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

4.2 Clinical Microbiology

See section 6.1.10.

4.3 Preclinical Pharmacology/Toxicology

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

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

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

See Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

See Biopharmaceutics review.

4.4.3 Pharmacokinetics

See Biopharmaceutics review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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

5.2 Review Strategy

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

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

All three studies were used in the safety analysis.

5.3 Discussion of Individual Studies/Clinical Trials

Study C-07-40

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

Study Design

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

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

Study Plan

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

[a] The Day 4 (EOT)/Exit Visit was conducted 12 to 48 hours after the last study dose and was performed by an ophthalmologist sub-investigator at sites where the principal investigator was a non-ophthalmologist.
[b] If a patient exited prior to the Day 4 (EOT)/Exit Visit, an Early Exit Visit was conducted that included all Day 4 procedures. This exam was performed within 24 hours of exit by an ophthalmologist Sub-Investigator at sites where the principal investigator was a non-ophthalmologist.
[c] Assent collected for patients over 6 and under 18 years of age, if applicable
[d] For women of child-bearing potential, UPT done before instillation of drug and at study exit.
[e] Specimens were collected prior to the fundus exam.
[f] All Day 1 (Screening/Baseline) Visit and Day 4 fundus examinations by Ophthalmologist utilized pupil dilation. All Day 1 (Screening/Baseline) Visit non-ophthalmologist fundus exams were undilated. A red reflex fundus exam was conducted in infants and uncooperative children.
[g] After dosing
[h] As needed

Inclusion Criteria

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

Exclusion Criteria

1. Signs and symptoms of bacterial conjunctivitis for longer than 4 days prior to Day 1 (Screening/Baseline) Visit
2. Abnormal findings in the posterior pole of the retina or any media opacity found in a fundus examination at the Day1 (Screening/Baseline) Visit
3. Presence of inflammation and/or active structural change in the cornea, iris, anterior chamber or lens at the Day 1 (Screening/Baseline) Visit
4. Presence of corneal opacity or any corneal abnormality at the Day 1 (Screening/Baseline) Visit that would impact the outcome of the study
5. Presence of concomitant viral infection
6. Presence of nasolacrimal duct obstruction at Day 1 (Screening/Baseline) Visit
7. Infants who had suspected or confirmed ophthalmia neonatorum of gonococcal, Chlamydia, herpetic or chemical origin
8. Infants whose birth mothers had any sexually transmitted disease within 1 month prior to delivery
9. Infants who were undergoing treatment for retinopathy of prematurity

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

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

Primary Efficacy Variable (s)

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

Secondary Efficacy Variable (s)

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

Primary Efficacy Analysis

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

Investigators

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

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

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

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

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

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

*Dr. Scott Petermann replaced Dr. Alberto Garcia as the Principal Investigator.
Note: each investigator who was not an ophthalmologist had an ophthalmologist as a sub-investigator.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

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

6.1.1 Methods

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

6.1.2 Demographics

Patient Demographics

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

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

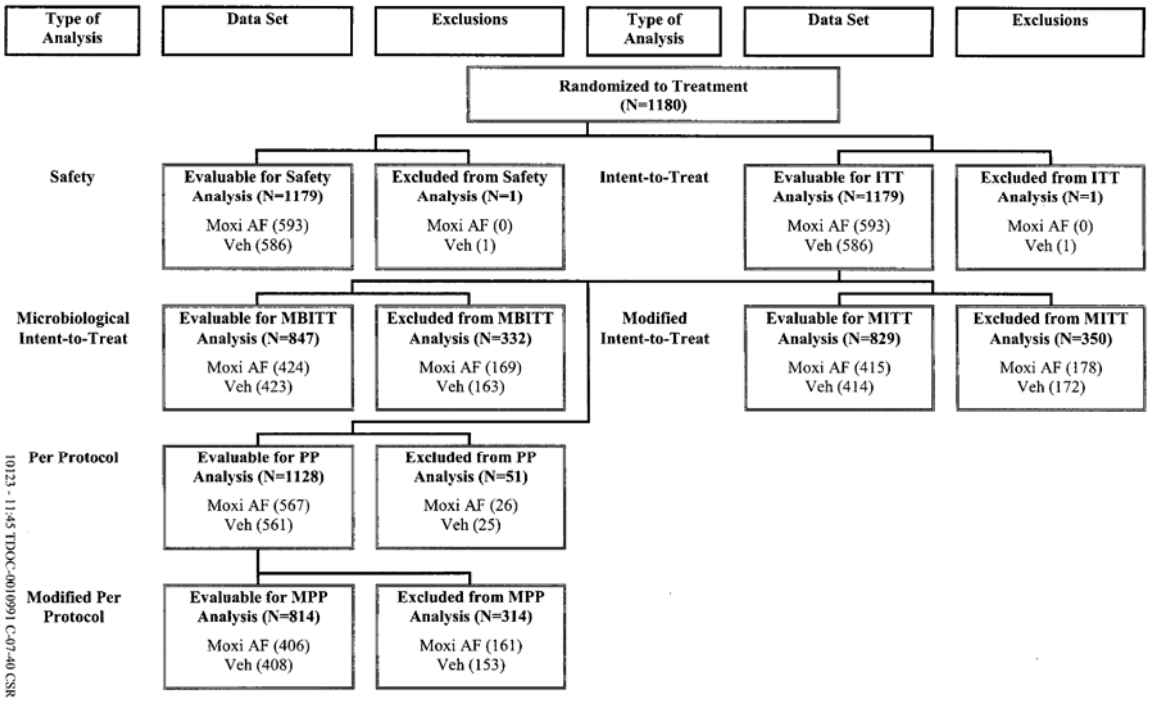
	Total N (%)	Moxi AF N (%)	Vigamox N (%)	Vehicle N (%)
Total	**2535 (100.0)**	**1270 (100.0)**	**349 (100.0)**	**916 (100.0)**
Age				
Infants (≥ 1 to < 2 months)*	8 (0.3)	1 (0.1)	2 (0.6)	5 (0.5)
Infants (≥ 2 to < 3 months)	4 (0.2)	3 (0.2)	0 (0.0)	1 (0.1)
Infants (≥ 3 to < 4 months)	7 (0.3)	3 (0.2)	0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

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

6.1.3 Subject Disposition

Study C-07-40 Subject Disposition

Figure 11.1.-1:
Disposition of Patients Enrolled in C-07-40



6.1.4 Analysis of Primary Endpoint(s)

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

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

Analysis Populations:

Safety: All patients who received drug.

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

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

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

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

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

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

Study C-07-40

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

p-value	0.0005	0.0006	0.0002	0.0015	0.0005

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

Reviewer's Comments:

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

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

6.1.5 Analysis of Secondary Endpoints(s)

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

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

Reviewer's Comments:

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

6.1.6 Other Endpoints

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

Study C-07-40

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

Reviewer's Comments:

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

6.1.7 Subpopulations

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

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

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

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

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

Reviewer's Comments:

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

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

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

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

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

6.1.10 Additional Efficacy Issues/Analyses

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

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

* Efficacy for this organism was found in fewer than 10 infections.
[1] Includes *Staphylococcus capitis subspecies capitis* (3), *S. capitis* (22); eradication rate 100% and 96 % respectively.
[2] Includes *Staphylococcus hominis ss. novobiosepticus* (4), *S. hominis* (6); eradication rate 100%.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

7.1.2 Categorization of Adverse Events

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

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

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

7.2 Adequacy of Safety Assessments

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

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

Overview of Exposure to Study Drug by Protocol

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

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

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

Reviewer's Comments:

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

7.2.2 Explorations for Dose Response

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

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with Moxifloxacin AF.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

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

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

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

7.3.3 Dropouts and/or Discontinuations

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

Moxi AF = Moxifloxacin AF

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

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

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

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

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

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

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

7.3.4 Significant Adverse Events

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

7.3.5 Submission Specific Primary Safety Concerns

N/A – No specific safety issues identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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

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

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

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

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

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

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

Headache	0	0	6	1.8
General disorders and administration site conditions				
Pyrexia	2	0.6	4	1.2

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

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

7.4.2 Laboratory Findings

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

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

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

7.4.3 Vital Signs

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

7.4.4 Electrocardiograms (ECGs)

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

7.4.5 Special Safety Studies/Clinical Trials

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

7.4.6 Immunogenicity

N/A – Immunogenicity testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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

7.5.2 Time Dependency for Adverse Events

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

7.5.3 Drug-Demographic Interactions

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

7.5.4 Drug-Disease Interactions

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

7.5.5 Drug-Drug Interactions

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

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

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

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

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

7.7 Additional Submissions / Safety Issues

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

8 Postmarket Experience

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

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

9 Appendices

9.1 Literature Review/References

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

9.2 Labeling Recommendations

See labeling recommendations which follow in the attached label.

9.3 Advisory Committee Meeting

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

10 Page(s) of Draft Labeling Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LUCIOUS LIM
11/19/2010

WILLIAM M BOYD
11/19/2010