

**Division of Anti-Infective and Ophthalmology Products
Advisory Committee Meeting
Briefing Package**

for

**Besifloxacin hydrochloride ophthalmic suspension for
the treatment of bacterial conjunctivitis**

Sponsor: Bausch & Lomb, Inc.
1400 North Goodman Street
Rochester, NY 14609-3547

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Introduction and Background

Besifloxacin hydrochloride ophthalmic suspension is an 8-chloro fluoroquinolone anti-infective and is a new chemical entity. It is being developed for topical ophthalmic use for the treatment of bacterial conjunctivitis and is not approved for marketing anywhere in the world.

The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division.

Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication, Dose, Regimens

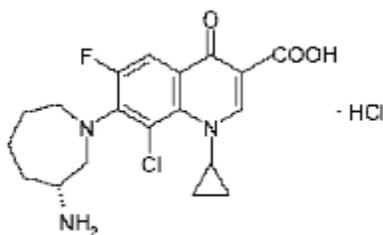
Proposed Proprietary Name:	Optura
Established name:	besifloxacin hydrochloride ophthalmic suspension
Sponsor:	Bausch & Lomb, Inc. 1400 North Goodman Street Rochester, NY 14609-3547
NDA Drug Classification:	S
Pharmacologic Category	Fluoroquinolone anti-infective; New Chemical Entity
Proposed Indication	For the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: <u>Aerobic and facultative Gram-positive microorganisms:</u> <i>CDC coryneform group G; Corynebacterium pseudodiphtheriticum*</i> ; <i>Corynebacterium striatum*</i> ; <i>Staphylococcus aureus</i> ; <i>Staphylococcus epidermidis</i> ; <i>Staphylococcus hominis*</i> ; <i>Staphylococcus lugdunensis*</i> ; <i>Streptococcus mitis group</i> ; <i>Streptococcus oralis</i> ; <i>Streptococcus pneumoniae</i> ; <i>Streptococcus salivarius*</i> <u>Aerobic and facultative Gram-negative microorganisms:</u> <i>Haemophilus influenzae</i> ; <i>Moraxella lacunata*</i> *Efficacy for this organism was studied in fewer than 10 infections.
Dosage Form and Route of Administration	topical ophthalmic suspension One drop in the affected eye(s) three times a day for seven days

State of Armamentarium for Indication

Ophthalmologic 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, chloramphenicol ophthalmic solution and moxifloxacin ophthalmic solution.

Chemical Composition

Besifloxacin hydrochloride ophthalmic suspension, 0.6% as base, is a sterile ophthalmic suspension. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use.



$C_{19}H_{21}ClFN_3O_3 \cdot HCl$
Mol Wt 430.30

Chemical Name: 7-[(3R)-3-Aminohexahydro-1H-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid monohydrochloride.

Each mL Contains:

Active: besifloxacin 0.6% (6 mg/mL);

Preservative: benzalkonium chloride 0.01%

Inactives: polycarbophil, mannitol, poloxamer 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide and purified water.

It is an isotonic suspension with an osmolality of approximately 290 mOsm/kg.

Human Pharmacokinetics

Plasma concentrations of besifloxacin were measured in adult male and female patients with suspected bacterial conjunctivitis who received besifloxacin bilaterally three times a day (16 doses total). Following the first and last dose, the maximum plasma besifloxacin concentration in each patient was less than 1.3 ng/mL. The mean besifloxacin C_{max} was 0.37 ng/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma was estimated to be 7 hours.

The concentration of besifloxacin in tear fluid was measured in healthy adult subjects who had received a single drop. Following the single administration, the mean besifloxacin C_{max} in tear samples was 610 $\mu\text{g/g}$ and the estimated total exposure (AUC 0-24h) was 1,232 $\mu\text{g}\cdot\text{h/g}$. The mean besifloxacin concentration observed in samples collected 24 hours after a single administration was 1.6 $\mu\text{g/g}$.

Description of Clinical Data Sources

Clinical Studies for the Ophthalmic Indication bacterial conjunctivitis for besifloxacin hydrochloride ophthalmic suspension

The applicant conducted three adequate and well controlled clinical trials. Studies #373 and #433, were superiority trials, and Study #434 was an equivalence trial comparing Optura (besifloxacin hydrochloride ophthalmic suspension, 0.6%) to Vigamox (moxifloxacin hydrochloride ophthalmic solution 0.5%).

Table of Clinical Studies for Safety and Efficacy

Type of Study	Study #	Study Design / Type of Control	Study Objective(s)	Products: Dosing; Route of Administration	Number of Subjects	Diagnosis	Treatment Duration	Primary Endpoint
Safety and Efficacy	373	Multicenter randomized, double-masked parallel Vehicle	Evaluate clinical and microbial efficacy of test product vs. vehicle in treatment of bacterial conjunctivitis	Besifloxacin hydrochloride, ophthalmic suspension, 0.6% as base Vehicle of besifloxacin ophthalmic suspension TID for 5 days: topical ocular	269 (137-study drug, 132 vehicle) / 256 (134 study drug, 122 vehicle) completed	Clinical diagnosis of bacterial conjunctivitis	5 days	Clinical resolution and eradication of baseline bacterial infection at Day 8
Safety and Efficacy	433	Multicenter randomized, double-masked parallel	Evaluate clinical and microbial efficacy of test product	Besifloxacin hydrochloride, ophthalmic suspension, 0.6% as base	957 (473-study drug, 484 vehicle) / 874 (442	Clinical diagnosis of bacterial conjunctivitis	5 days	Clinical resolution and eradication of baseline bacterial infection at Day 5

		Vehicle	vs. vehicle in treatment of bacterial conjunctivitis	Vehicle of besifloxacin ophthalmic suspension TID for 5 days: topical ocular	study drug, 432 vehicle) completed			
Safety and Efficacy	434	Multicenter randomized, double-masked parallel Active	Evaluate clinical and microbial efficacy of test product vs. control in treatment of bacterial conjunctivitis	Besifloxacin hydrochloride, ophthalmic suspension, 0.6% as base Vigamox – moxifloxacin HCL ophthalmic solution 0.5% as base TID for 5 days: topical ocular	1161 (582-study drug, 579 vehicle) / 1109 (555 study drug, 554 vehicle) completed	Clinical diagnosis of bacterial conjunctivitis	5 days	Clinical resolution and eradication of baseline bacterial infection at Day 5

Discussion of Individual Trials

Safety and Efficacy Trials:

I. Study #: 373

Title: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 (Besifloxacin hydrochloride ophthalmic suspension, 0.6%) Compared to Vehicle in the Treatment of Bacterial Conjunctivitis

Selection of Patient Population

Inclusion Criteria

Subjects were enrolled in the study if they satisfied the following criteria:

1. Must be at least one year old.
2. Must have signature of subject or legally authorized representative (if subject is under 18 years of age) on the Informed Consent Form.
3. Must have signature of subject on the Assent Form if subject is 6 to 17 years old.
4. Must have a clinical diagnosis of acute bilateral bacterial conjunctivitis and exhibit purulent conjunctival discharge (crusty or sticky eyelids) and redness in at least one eye. A minimum score of 1 should be present for discharge and a minimum score of 1 for either bulbar or palpebral conjunctival injection.
5. Must have pin-holed visual acuity equal to or better than 20/200 in both eyes. Age-appropriate visual acuity was to be performed. Every effort was made to obtain a visual acuity measurement in children. If Visual acuity was unobtainable in children, it was at the investigator's discretion to meet inclusion criteria.
6. Must be willing to discontinue contact lens wear for the duration of the study.
7. Must be willing to avoid disallowed medications during the study period. Disallowed medications include any systemic or topical antimicrobial medication, and any medication that the Investigator feels may interfere with the study parameters.
8. Must understand the scope of the study including completion of the worksheet and be willing to follow instructions and be able to make all required study visits.
9. Must be willing to avoid disallowed medications during the study period. Disallowed medications included any systemic or topical antimicrobial medication, and any medication that the Investigator felt might interfere with the study parameters.
10. Must understand the scope of the study including completion of diary, be willing to follow instructions, and be able to make all required study visits.

11. If subject is a female of childbearing potential, she must utilize reliable contraceptive methods and have a negative urine pregnancy test.

Exclusion Criteria

Subjects were excluded from the participation in the study if they fulfilled any one of the following criteria:

The following are exclusion criteria for prospective study subjects:

1. Any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, diabetes, or cystic fibrosis).
2. Use of topical ophthalmic solutions, including tear substitutes, within two hours before and during the study.
3. Use of any ophthalmic topical anti-inflammatory agents within 48 hours before and during the study.
4. Subjects likely to require antimicrobial therapy with any active respiratory tract infection, urinary tract infection, skin/soft tissue infection, or otitis media.
5. Pregnant or nursing females. This is designed to minimize risks of drug delivery to fetus and/or infants.
6. Known hypersensitivity to SS-734 or to any of the ingredients in the study medication.
7. Known hypersensitivity to fluoroquinolones or to any of the ingredients in the study medication.
8. Ocular surgery (including laser surgery) in either eye within the past six weeks.
9. Subjects with suspected viral or allergic conjunctivitis (i.e., severe itching or acute follicular conjunctivitis), or any other disease conditions that could interfere with the efficacy and safety evaluations of the study medication.
10. Subjects with suspected iritis (i.e., smaller pupil, pain, and photophobia in infected eye).
11. History of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome.
12. Use of any antibiotic within 72 hours of enrollment.
13. Any active ulcerative keratitis, specifically any epithelial loss greater than punctate keratitis (e.g., confluent epithelial loss or any infiltration).
14. Participation in an ophthalmic drug or device research study within the 30 days prior to entry in this study.
15. Subjects who were immune compromised.

Study Procedures

Visit	Study Period	Hx ¹	Visual Acuity	Biomi-croscopy	Direct Ophthal-moscopy	Dispense Drug ²	Instill Drug at Site	Microbial Culture	Clinical Obser-Vation ⁴
1	Day 1	X	X	X	X	X	X	X	X
2	Day 4 (±1)		X	X			X	X ³	X

	day)								
3	Day 8 (±1 day)		X	X	X			X ³	X

¹ Hx = general history

² The first Day 1 dose of study medication was administered in the office after the initial eye exam and conjunctival culture. Subjects were instructed to administer the study medication at six-hour intervals using the appropriately labeled bottle (subjects were instructed to instill all three doses on Day 1 even if the intervals were shorter than six hours). Subjects were instructed not to dose the medications on the morning of their Visit 2 (Day 4) office visit; the study medication was administered in the office after the eye exam and conjunctival culture. A subject diary was used to record study medication instillation times.

³ Microbial culture – culture of the conjunctiva in the infected eye(s) was measured using a 0-3 scale:

0a. Eradication (infecting organism originally present at or above threshold on Day 1 and absent in follow-up culture without new isolate at or above threshold)

0b. Eradication (infecting organism originally present at or above threshold on Day 1 and absent in follow-up culture with new isolate present at or above threshold)

1a. Reduction (infecting organism originally present at or above threshold on Day 1 and reduced to a count below threshold in follow-up culture without a new isolate at or above threshold)

1b. Reduction (infecting organism originally present at or above threshold on Day 1 and reduced to a count below threshold in follow-up culture with a new isolate present at or above threshold)

2a. Persistence (infecting organism originally present at or above threshold on Day 1 and not exceeding Day 1 count, but remains above or equal to threshold in follow-up culture without new isolate at or above threshold)

2b. Persistence (infecting organism originally present at or above threshold on Day 1 and not exceeding Day 1 count, but remains above or equal to threshold in follow-up culture with new isolate present at or above threshold)

3a. Proliferation (infecting organism originally present at or above threshold on Day 1 and is increased above Day 1 count in follow-up culture) without a new isolate at or above threshold

3b. Proliferation (infecting organism originally present at or above threshold on Day 1 and is increased above Day 1 count in follow-up culture) with a new isolate present at or above threshold

⁴ Clinical observation - Investigator ratings of ocular discharge and bulbar/palpebral conjunctival injection using a 0-3 scale in both eyes. Standardized photographs were used to grade conjunctival injection. At Visits 2 and 3, Investigators rated overall global changes on a 0-3 scale indicating if the condition had been cured (0), improved (1), not changed (2) or worsened (3).

Efficacy Variable

The primary efficacy endpoints were clinical resolution and eradication of baseline bacterial infection at Visit 3. Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. All subjects who were randomly assigned to treatment and had bacteriologically confirmed conjunctivitis were evaluated for the primary endpoints in the intent-to-treat analyses.

Subjects Enrolled: Study # 373

A study to evaluate the clinical and microbial efficacy and safety of 0.6% ISV-403 (Besifloxacin hydrochloride ophthalmic suspension, 0.6%) compared to Vehicle in the treatment of bacterial conjunctivitis. (Enrolled/Culture Positive/Cure)

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
001	Holland, Edward, M.D.	Edgewood, KY 41017	0	1/0/0
002	Aldridge, Charles, OD	Burnsville, NC 80525	7/2/2	7/1/0
003	Arnold, Patrick, M.D.	Fort Collins, CO 80525	4/3/2	3/2/1
004	Caldwell, Delmar, M.D.	New Orleans, LA 70112	1/0/0	0
005	Carey, Timothy, M.D.	Seattle, WA 98105	1/0/0	1/0/0
006	Cedrone, Ronald, O.D.	Falmouth, ME	2/1/1	2/1/0
007	Choate, Walter, O.D.	Madison, TN 37115	6/3/1	5/2/0
010	Davis, Richard, M.D.	Huntington, NY 11743	2/1/0	2/0/0
011	Day, Douglas, M.D.	Atlanta, GA 30342	1/0/0	2/0/0
012	DePaolis, Michael, O.D.	Rochester, NY 14618	6/4/1	6/2/0
013	Dhingra, Ajeet, M.D.	Decatur, GA 30030	2/1/1	3/2/1
016	Hobbs, Thomas, O.D.	Warrensburgh, MO 64093	2/1/1	3/2/1
017	Hunter, Judy, M.D.	Torrance, CA 90503	8/4/4	9/3/2
018	Karpecki, Paul, O.D.	Kansas City, MO 64154	2/1/0	2/0/0
021	Markoff, Joseph, M.D., PhD.	Pholadelphia, PA 19148	6/2/0	6/3/1
022	Moody, Kurt, O.D.	Kingston, PA 18704	5/2/2	4/2/2
023	Onofrey, Bruce, O.D.	Albuquerque, NM 87109	1/1/0	0
024	Perez, Bernard, M.D.	Tampa, FL 33603	4/2/2	5/4/3
025	Rotberg, Michael, M.D.	Charlotte, NC 28210	4/1/0	3/0/0
026	Rubin, Benjamin, M.D.	Potomac, MD 20854	3/1/0	1/1/0
027	Vicksman, Sherwyn, O.D.	Denver, CO 80246	6/0/0	6/4/2
028	White, Eric, O.D.	Zachary, LA 70791	0	0
029	Whitsett, Jeffrey, M.D.	Houston, TX 77055	1/0/0	1/0/0
030	Wolstan, Barry, M.D.	Torrance, CA 90503	3/2/1	2/0/0
031	Ziegler, David, O.D.	West Allis, WI 53227	7/2/2	7/1/1
033	Rigel, Lee, O.D.	East Lansing, MI 48236	15/7/5	15/7/2
034	Slade, Stephen, M.D.	Houston, TX 77027	2/1/1	2/1/0
035	Boucher, James, O.D.	Laramie, WY 82070	2/2/2	2/1/1
036	Katz, Randy, M.D.	Boynton Beach, FL 33426	1/1/1	0
037	Steigemeier, Mary Jo, O.D.	Beachwood, OH 44122	1/1/1	0
038	Tepedino, Michael., M.D.	High Point, NC 27262	4/1/1	3/1/0
040	Klessman, Jay, O.D.	Washington, DC 20006	1/0/0	0
047	Greenberg, Michael, O.D.	Chagrin Falls, OH 44023	1/1/0	2/1/0
049	Cooper, Stephen, M.D.	Shreveport, LA 71105	2/2/2	2/2/1
053	Wexler, Jeffrey, M.D.	Columbia, MD 21044	0	1/1/1

II. Study #: 433

Title: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 (Besifloxacin hydrochloride ophthalmic suspension, 0.6%) Compared to Vehicle in the Treatment of Bacterial Conjunctivitis

Selection of Patient Population

Inclusion Criteria

Subjects were eligible if they met all the following criteria:

1. Must have been at least 1 year of age.
2. Must have had the signature of the subject or legally authorized representative (if the subject was under 18 years of age) on the ICF.
3. Must have had the signature of the subject providing assent, if the subject was 6 to 17 years of age.
4. Must have had a clinical diagnosis of acute bacterial conjunctivitis and exhibited purulent conjunctival discharge (crusty or sticky eyelids) and redness in at least 1 eye. A minimum score of 1 should have been present for discharge and a minimum score of 1 for bulbar conjunctival injection.
5. Must have had pin-holed VA equal to or better than 20/200 in both eyes. Age appropriate VA testing was performed. Every effort should have been made to obtain a VA measurement in children. If VA was unobtainable in children, it was at the Investigator's discretion if the child met inclusion.
6. Must have been willing to discontinue contact lens wear for the duration of the study.
7. Must have been willing to avoid disallowed medications during the study period. Disallowed medications included any systemic or topical antimicrobial medication, and any medication that the Investigator felt could interfere with the study parameters.
8. Must have understood the scope of the study including completion of the subject worksheet and willingness to follow instructions and make all required study visits.
9. If subject was a female of childbearing potential, she must have utilized reliable contraceptive methods and had a negative pregnancy test.

Exclusion Criteria

Subjects were excluded from the study if they met any of the following criteria:

1. Any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, diabetes, or cystic fibrosis).
2. Use of topical ophthalmic solutions, including tear substitutes, within 2 hours before and during the study.
3. Use of any ophthalmic topical anti-inflammatory agents within 48 hours before and during the study.
4. Subjects who were likely to require antimicrobial therapy with any active respiratory tract infection, urinary tract infection, skin/soft tissue infection, or otitis media.

5. Pregnant or nursing females. This criteria was designed to minimize risks of drug delivery to fetus and/or infants.
6. Known hypersensitivity to SS734 or to any of the ingredients in the study medications.
7. Known hypersensitivity to fluoroquinolones or to any of the ingredients in the study medications.
8. Ocular surgery (including laser surgery) in either eye within the past 6 weeks.
9. Subjects with suspected viral or allergic conjunctivitis (i.e., severe itching or acute follicular conjunctivitis), or any other disease conditions that could have interfered with the efficacy and safety evaluations of the study medication.
10. Subjects with suspected iritis (i.e., smaller pupil, pain, and photophobia in infected eye).
11. History of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome.
12. Use of any antibiotic within 72 hours of enrollment.
13. Any active ulcerative keratitis, specifically any epithelial loss greater than punctate keratitis (e.g., confluent epithelial loss or any infiltration).
14. Participation in an ophthalmic drug or device research study within the 30 days prior to entry in this study.
15. Subjects who were immune compromised.

Study Procedures

	Visit 1 Day 1	Visit 2 Day 5 (±1 day)	Visit 3 Day 8(1 day)
Informed Consent and HIPAA Authorization	X		
Demographics	X		
Current and Relevant Medical and Ocular History	X		
Pregnancy	X		
Visual Acuity	X	X	X
Biomicroscopy	X	X	X
Direct Ophthalmoscopy	X		X
Microbial Cultures	X	X	X
Clinical Assessment of Bacterial Conjunctivitis	X	X	X
Investigator's Global Assessment of Changes		X	X
Adverse Events¹	X	X	X
Concomitant Medications	X	X	X
Dispense Drugs²	X		
Instill Drug at Site	X	X	
Weigh Medication Bottle(s)	X	X	X
Study Exit³			X

¹ AEs were collected from the time of informed consent to study exit.

² The first Day 1 dose of study medication was instilled in the office after the initial eye exam and conjunctival culture. Subjects were instructed to instill the study medication at approximately six-hour intervals

using the appropriately labeled bottle (subjects were instructed to instill all three doses on Day 1 even if the intervals were shorter than six hours). Subjects were instructed not to instill study drug on the morning of their Visit 2 (Day 5) office visit; the study medication was instilled in the office after the eye exam and conjunctival culture. Subjects were instructed to record study medication instillation dates and times on worksheets provided by the Sponsor.

³ All study medication bottle(s) were collected at this visit.

Efficacy Variable

The primary efficacy endpoints were the following:

- Clinical resolution after 5 days of treatment. Clinical resolution was defined as the absence of both ocular discharge and bulbar conjunctival injection at Visit 2 (Day 5 ±1 day).
- Microbial eradication of baseline bacterial infection after 5 days of treatment. Microbial eradication was defined as the absence at Visit 2 (Day 5 ±1 day) of all accepted ocular bacterial species that were present at or above threshold at baseline.

Subjects Enrolled : Study # 433

A study to evaluate the clinical and microbial efficacy and safety of 0.6% ISV-403 (Besifloxacin hydrochloride ophthalmic suspension, 0.6%) compared to Vehicle in the treatment of bacterial conjunctivitis. (Enrolled/Culture Positive/Cure)

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
663476	Abrams, Marc, M.D.	Cleveland, OH	4/2/2	5/2/1
664475	Andrews, Wilson, M.D	Woodstock, GA	6/1/1	6/1/1
731410	Aquavella, James, M.D.	Rochester, NY	6/3/3	6/4/2
492619	Arnold, Patrick, M.D.	Fort Collins, CO	13/10/10	14/12/11
719422	Beck, William, M.D.	Newton, KS	14/7/6	14/6/5
667472	Brasher, Craig, M.D. / Lam, Toan, M.D	Salt Lake City, UT	4/1/1	3/1/1
668471	Brown, Christopher, M.D.	Teaneck, NJ	3/1/1	3/2/0
462648	Brown, David, M.D.	Fort Myers, FL	3/0/0	4/0/0
694446	Capoor, Seema, M.D.	Lexington, KY	4/2/2	4/3/2
670469	Cardona, David, M.D.	Fresno, CA	10/1/1	11/1/0
599539	Cooper, Stephan, M.D.	Shreveport, LA	30/12/11	31/8/7
884270	Cottingham, Andrew, M.D.	San Antonio, TX	4/1/0	3/0/0
722419	Dao, Jung, M.D.	Phoenix, AZ	13/5/5	12/5/3
672419	Dawson, Peter, M.D.	Houston, TX	1/0/1	0
697443	De Leon, Jose, M.D.	Paramount, CA	25/14/13	25/5/3
231868	Donshik, Peter, M.D.	Bloomfield, CT	1/1/1	0

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
862292	Eiferman, Richard, M.D.	Louisville, KY	4/2/2	5/3/1
740401	Galiani, David, M.D. / Kay, Michael, M.D.	Philadelphia, PA	1/0/0	0
698442	George, F, M.D.	Jonesboro, AK	18/6/4	19/7/5
674465	Gonzalez, Casimiro, M.D.	Cudahy, CA	1/0/0	0
723418	Gorovoy, Mark, M.D.	Fort Myers, FL		
675464	Hamouche, Nicolas, M.D.	Ames, IA	4/2/2	5/2/1
213868	Hanlom, Paul, O.D.	Rochester, NY	1/1/1	2/0/0
676463	Harral, Russell, O.D.	Jonesboro, AR	9/3/2	10/2/1
725416	Heller, Warren, M.D.	Phoenix, AZ	39/22/21	39/18/11
734007	Henderson, Thomas, M.D.	Austin, TX	2/0/0	3/0/0
502609	Hunter, Judy, M.D.	Torrance, CA	6/0/0	7/3/2
735406	Johnson, David, M.D.	Wilmington, NC	13/4/4	13/7/5
726415	Jorizzo, Paul, M.D.	Medford, OR	5/1/0	4/2/1
700440	Kanengiser, Bruce, M.D.	Piscataway, NJ	36/22/15	35/19/16
702438	Kohl, Douglas, M.D.	Boca Raton, FL	1/0/0	2/0/0
677462	Kushner, Floyd, M.D.	Daytona Beach, FL	1/0/0	2/1/1
678461	Lemley, Heath, M.D.	Morgantown, WV	6/2/2	6/2/2
449658	Lindahl, Kenneth, M.D.	Rochester, NY	4/2/2	3/1/1
704436	Maguen, Ezra, M.D.	Los Angeles, CA	4/1/1	4/1/1
506942	Markoff, Joseph, M.D.	Philadelphia, PA	8/5/5	8/4/3
706434	Mauger, Thomas, M.D.	Columbus, OH	3/0/0	2/2/1
727414	Merkley, Kevin, M.D.	Salt Lake City, UT	4/2/2	6/2/1
707433	Mitchell, Elizabeth, M.D.	Memphis, TN	2/2/1	2/0/0
681458	Ottman, David, M.D.	Carmichael, CA	0	1/1/1
683540	Perez-Becerra, Jose, M.D.	San Antonio, TX	20/7/4	20/7/5
755461	Powell, Stephen, M.D.	Oakland, MD	1/0/0	0
709431	Rich, Cadmus, M.D.	Raleigh, NC	4/2/2	4/0/0
685455	Rubin, Jay, M.D.	San Antonio, TX	5/1/1	4/1/1
710430	Sanchez-Bal, Victoria, M.D.	Bellflower, CA	10/5/5	12/6/4
729412	Schenkel, Eric, M.D.	Easton, PA	1/1/0	0
712429	Schulman, David, M.D.	San Antonio, TX	3/2/1	4/2/2
713428	Spector, Steve, M.D.	West Palm Beach, FL	5/2/1	5/2/1
714427	Sprague, Amy, M.D.	Augusta, GA	4/2/2	4/2/1
426680	Stiegemeier, Mary, M.D.	Beachwood, OH	6/1/1	4/1/1
715426	Sutherland, John, M.D.	Waterloo, IA	19/8/5	20/7/2
687453	Tachibana, Mikio, M.D.	Fountain Valley, CA	13/9/9	13/10/10
591545	Tepedino, Michael, M.D.	High Point, NC	36/11/8	36/13/9
688452	Tibbets, John, M.D.	Bangor, ME	5/2/1	5/2/2
717424	Weston, Jon-Marc, M.D.	Roseburgh, OR	20/8/6	19/6/5
225874	White, Eric, M.D.	San Diego, CA	1/1/1	2/1/0

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
690450	Yee, Richard, M.D.	Houston, TX	7/0/0	6/1/0
691449	Zosa, Noli, M.D.	Pico Rivera, CA	2/1/1	2/0/0

III. Study #: 434

Title: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 (Besifloxacin hydrochloride ophthalmic suspension, 0.6%) Compared to Vigamox in the Treatment of Bacterial Conjunctivitis

Selection of Patient Population

Inclusion Criteria, Exclusion Criteria and Study Procedures

Study #434 had same Inclusion and Exclusion Criteria and Study Procedures as in Study #433 (listed above).

Efficacy Variable

The primary efficacy endpoints for Study #434 were the same as Study #433 (listed above):

Subjects Enrolled : Study # 434

A study to evaluate the clinical and microbial efficacy and safety of 0.6% ISV-403 (Besifloxacin hydrochloride ophthalmic suspension, 0.6%) compared to Vigamox in the treatment of bacterial conjunctivitis. (Enrolled/Culture Positive/Cure)

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
692448	Adkins, Jeffery, M.D.	Carmichael, CA	3/2/2	3/1/1
808338	Arora, Chandra, M.D	Marion, OH	2/2/1	1/0/0
748395	Asbell, Penny, M.D.	New York, NY	3/0/0	3/0/0
749394	Au, Yue-Kong, M.D.	Bossier City, LA	2/1/0	1/0/0
852302	Bacharach, Jason, M.D.	Petaluma, CA	3/0/0	4/3/3
764380	Balkan, Robert, M.D.	Metairie, LA	1/0/0	0
809337	Baumann, Jeffrey, M.D.	Mount Dora, FL	1/0/0	2/0/0
760384	Beavers, John, M.D.	Oklahoma City, OK	15/6/5	14/7/7

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
720421	Bluestein, Ettaleah, M.D.	Charlestown, SC	4/0/0	6/2/1
695445	Cowden, John, M.D.	Columbia, MO	4/3/3	4/3/3
789356	Curnyn, Kimberlee, M.D.	Hoffmann Estates, IL	3/2/2	2/1/1
761383	D'Aversa, Gerard, M.D.	Valley Stream, NY	5/1/0	6/3/3
767378 / 860294	Dang, N. Yen, M.D. / Davis, Romana, M.D.	Little Rock, AK	2/2/0	1/0/0
497614	Davis, Richard, M.D.	Huntington, NY	4/1/1	3/3/1
696444	Davitt, William, M.D.	El Paso, TX	16/6/5	18/6/6
739402	Denison, Chad, M.D.	Hutchinson, NY	14/11/10	13/5/2
803343	DeSai, Komal, M.D.	Kansas City, MO	6/2/1	6/3/1
499612	Dhingra, Ajeet, M.D.	Decatur, GA	3/1/1	3/0/0
762382	Donnenfeld, Eric, M.D.	Rockville, NY	4/3/3	4/2/2
673466	Fagadau, Warren, M.D.	Dallas, TX	1/1/1	2/1/0
771374	Gancayco, Theodore, M.D.	Washington, DC	8/2/2	9/4/2
790355	Goyal, Dinesh, M.D.	Minneapolis, MN	0	1/1/1
791354	Grady, Frank, M.D.	Lake Jackson, TX	2/2/2	2/2/0
733408	Groat, Robert, M.D.	Greensboro, NC	2/0/0	2/0/0
758386	Hagen, Kerry, M.D.	Portland, OR	1/1/1	1/0/0
804342	Harris, Charles, M.D.	Savannah, GA	5/1/1	4/3/1
779366	Harris, Michael, M.D.	Livingston, NJ	11/4/4	10/7/5
775370	Janes, Charles, M.D.	Los Angeles, CA	1/0/0	2/1/1
776369	Katow, Jean, M.D.	Gardena, CA	1/0/0	1/1/1
504607	Katzman, Barry, M.D.	San Diego, CA	14/8/7	15/7/7
759385	Kurata, Fred, M.D.	Los Angeles, CA	4/0/0	4/2/2
834318	Lahners, William, M.D.	Sarasota, FL	1/1/1	0
754389	Latkany, Robert, M.D.	New York, NY	2/0/0	2/1/0
703437	Lillestol, Michael M.D.	Los Angeles, CA	2/1/1	2/0/0
580555	Lorenz, Douglas, M.D.	Henderson, NV	3/0/0	3/3/3
784361	Luchs, Jodi, M.D.	Wantagh, NY	7/4/4	7/6/6
794352	Luffey, Gary, M.D.	Ruston, LA	21/5/5	20/5/3
581554	Macy, Jonathan, M.D.	Los Angeles, CA	4/2/0	2/1/0
665474	Malhotra, Ranjan, M.D.	Carmichael, CA	23/13/12	22/8/6
777368	Marsico, Nicholas, M.D.	Torrance, CA	2/0/0	2/2/2
799347	McDavid, E. Chandler, M.D.	Sandersville, GA	2/1/1	2/0/0
837314	McDonald, Marguerite, M.D.	Lynbrook, NY	5/1/0	5/2/1
750393	McGriff, Buhilda, M.D.	Concord, NC	26/20/16	26/17/13
508604	Melton, Ron, O.D.	-	7/3/3	75/5
732409	Mohar, Dale, M.D.	Kerrville, TX	9/1/1	8/3/3
842556	Monica, Monica, M.D.	Gretna, LA	12/7/7	12/6/6
680459	Olander, Kenneth, M.D.	Maryville, TN	6/3/2	5/2/2

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
728413	Paul, Matthew, M.D.	Danbury, CT	8/1/1	9/5/4
797349	Pendleton, Robert, M.D.	Oceanside, CA	14/6/4	12/5/4
252853	Perez, Bernard, M.D.	Tampa, FL	14/9/6	14/7/6
752391	Protzko, Eugene, M.D.	Bel Air, MD	40/23/21	40/24/23
741573	Prywes, Arnold, M.D.	Bethpage, NY	0	1/1/0
508604	Rotberg, Michael, M.D.	Charlotte, NC	7/3/3	7/5/5
617521	Schachter, Scott, O.D.	Pismo Beach, CA	1/0/0	1/0/0
711585	Schechter, Scott, M.D.	Boynton Beach, FL	14/9/7	13/5/4
442665	Schenker, Howard, M.D.	Rochester, NY	24/13/12	25/14/13
769376	Shuster, Alan, M.D.	Jupiter, FL	2/1/0	4/2/1
833318	Silbert, David, M.D.	Lancaster, PA	1/1/1	0
490621	Silverstein, Steven, M.D.	Kansas City, MO	5/2/2	5/2/1
863291	Silverstein, Bruce, M.D.	Redding, CA	2/0/0	3/3/2
836316	Smith, Stephen, M.D.	Fort Myers, FL	4/2/1	4/3/2
751392	Stein, Emil, M.D.	Las Vegas, NV	15/6/6	15/7/5
264837	Stephenson, P., M.D.	Venice, FL	3/2/2	3/1/1
730411	Stewart, Robert, M.D.	Houston, TX	10/1/1	10/1/1
788357	Stone, Donald, M.D.	Oklahoma City, OK	2/0/0	3/1/1
742400	Sutton, James, M.D.	Ocean Springs, MS	1/1/1	2/1/1
778367	Tauber, Shachar, M.D.	Springfield, MO	20/9/9	19/9/6
765379	Tauber, Joseph, M.D.	Kansas City, MO	1/0/0	1/0/0
770375	Thom, Steven, M.D.	Fargo, ND	4/1/1	5/3/3
737404	Treft, Robert, M.D.	Layton, UT	4/2/2	4/4/3
382720	Udvari, Joseph, M.D.	Moon Township, PA	8/2/2	9/5/5
223876	Vicksman, Sherwyn, M.D.	Denver, CO	17/8/8	16/9/9
718423	Wiggins, Robert, M.D.	Asheville, NC	3/0/0	3/0/0
511601	Wolstan, Barry, M.D.	Torrance, CA	8/3/2	7/0/0
847306	Abano, Jessica, M.D.	Quezon City, Philippines	2/1/1	1/1/1
849305	Bhagat, Yasmin, M.D.	Mumbai, India	28/9/9	28/14/13
848949	Garg, Prashant, M.D.	Hyderabad, India	2/0/0	3/1/1
865289	Mathur, Uman, M.S.	New Dehli, India	10/1/1	11/7/5
866288	Prajna, N., M.B.B.S.	Tamilnadu, India	2/0/0	1/0/0
846307	Santos, Reynaldo, M.D.	Quezon City, Philippines	6/3/2	5/3/2
845308	Siong, Ruben, M.D.	Quezon City, Philippines	1/0/0	1/0/0
845309	Siong, Ruben, M.D.	Manila, Philippines	6/5/4	5/3/2
867287	Sony, Parul, M.D.	New Delhi, India	7/2/2	6/2/2
868286	Tandon, Radhika, M.D.	New Delhi, India	12/7/7	13/5/4
227872	Uy, Harvey, M.D.	Makati, Philippines	31/1	3/0/0

Integrated Review of Efficacy

Demographics

Demographics and Baseline Characteristics

Studies 373, 433 and 434
Safety population

	Besifloxacin (N=1192)	Besi Vehicle (N= 616)	Vigamox (N= 579)
Age (years)			
N	1192	616	579
Mean (SD)	31.5 (23.1)	28.7 (21.9)	36 (24.5)
Median	27.5	25.5	34
Min, Max	1, 98	0, 97	0, 100
Gender			
Male	471 (39.5%)	240 (39%)	257 (44.4%)
Female	721 (60.5%)	376 (61%)	322 (55.6%)
Race			
White	813 (68.2%)	422 (68.5%)	387 (66.8%)
Asian	98 (8.2%)	10 (1.6%)	89 (15.4%)
Black	123 (10.3%)	53 (8.6%)	67 (11.6%)
Other	158 (13.3%)	131 (21.3%)	35 (6.2%)
Age Distribution			
Less than 2 years	46 (3.9%)	21 (3.4%)	14 (2.4%)
2 to 9 years	221 (18.5%)	134 (21.8%)	91 (15.7%)
10 to 19 years	182 (15.3%)	103 (16.7%)	79 (13.6%)
20 to 29 years	175 (14.7%)	90 (14.6%)	76 (13.1%)
30 to 39 years	149 (12.5%)	91 (14.8%)	75 (13.0%)
40 to 49 years	134 (11.2%)	62 (10.1%)	63 (10.9%)
50 to 59 years	116 (9.7%)	53 (8.6%)	64 (11.1%)
60 years or older	169 (14.2%)	62 (10.1%)	117 (20.2%)

Disposition of Subjects Treatment and Post-treatment Periods

Dropouts and/or Discontinuations

	Study 373		Study 433		Study 434	
	Vehicle	Besifloxacin	Vehicle	Besifloxacin	Besifloxacin	Moxifloxacin
Randomized	132	137	484	473	582	579
Completed	122	134	432	442	555	554
Discontinued	10	3	52	31	27	25
Per Protocol	38	42	133	151	161	180
Intent-to-Treat	56	60	191	199	255	278
Primary Reason for Discontinuation						
Adverse Event	1		5	4	11	5
Protocol Violation	0	1				
Withdrew Consent	1		16	10	1	4
Lost to Follow-up	1	1	9	10	10	8
Lack of Efficacy	7	1	14	3	1	1
Other			8	4	4	7

Protocol Defined Analysis Populations

Analysis Populations

Three analysis populations were utilized:

- The Intent-to-Treat Population consisted of all subjects who had a clinical diagnosis of bacterial conjunctivitis, were randomized to treatment, and received at least one drop of the study medication.
- Modified Intent-to-Treat (mITT) population included all subjects who were randomized to treatment and who had received at least one drop of the study medication and had baseline cultures indicating pathogenic bacterial levels.
- The Per Protocol population, PP, were those intent-to-treat subjects who did not have a major protocol violation. The identification of subjects thus excluded from the per-protocol population was conducted masked to treatment allocation. The per-protocol population was only analyzed with respect to the primary efficacy variables.

Primary Efficacy Endpoint

Primary Efficacy Measurement

The primary efficacy measurements were the three clinical signs of bacterial conjunctivitis: ocular discharge, bulbar conjunctival injection, and palpebral conjunctival injection; and the primary efficacy measurement for microbial eradication was the presence of ocular bacterial species present at or above threshold at baseline.

Primary Efficacy Variable

The primary efficacy variable was clinical resolution defined as the absence (complete resolution) of all three clinical signs: ocular discharge, bulbar conjunctival injection, and palpebral conjunctival injection; and for microbial eradication was the absence of ocular bacterial species that had been present at or above a certain threshold at baseline.

Primary Efficacy Analysis

The primary efficacy analysis for clinical resolution and microbial eradication was the p-Value for Comparison of Treatments where the Cochran-Mantel-Haenszel test was calculated (stratified by center) and the Pearson chi-squared test.

Intent To Treat (i.e., not necessarily culture positive) – Clinical Resolution

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N=**	N=**	p=**
Clinical Resolution	(%)**	(%)**	
Visit 3 - Day 8 (+ 1 day)	N=136	N=130	CMH* p=0.0002
Clinical Resolution	89 (65%)	59 (45%)	

* Cochran-Mantel-Haenszel

** Data requested from sponsor – submission pending.

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)	N=456	N=457	p= 0.0056 / 0.0175 ¹
Clinical Resolution	195(43%)	160(35%)	(1.42%, 14.08%) ²
Visit 3 (Day 8 + 1 day)	N=461	N=463	p= <0.0001 / <0.0001 ¹
Clinical Resolution	379 (82%)	328 (71%)	(5.90%, 16.84%) ²

¹ p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.

² 95% CI for Difference in Percentages; Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 434	Besifloxacin	Moxifloxacin	
Visit 2 (Day 5 ± 1 day)	N=568	N=566	p= 0.8827 / 0.8575 ¹
Clinical Resolution	321 (57%)	323 (57%)	(-6.33%, 5.22%) ²
Visit 3 (Day 8 + 1 day)	N=572	N=569	p= <0.8393 / >0.9999 ¹
Clinical Resolution	488 (85%)	123 (85%)	(-4.20%, 4.01%) ²

¹ p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.

² Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin

Reviewer's Comments:

Although not necessary to support approval, besifloxacin ophthalmic suspension was superior to its vehicle in the Intent-to-Treat population in Studies #373 and # 433 and was equivalent to the moxifloxacin populations.

Modified Intent To Treat (i.e., culture positive) – Clinical Resolution

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N=60	N=56	CMH* p=0.3144
Clinical Resolution	14 (23%)	8(14%)	
Visit 3 - Day 8 (+ 1 day)	N=60	N=56	CMH* p=0.0013
Clinical Resolution	37 (62%)	20 (36%)	

* Cochran-Mantel-Haenszel

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)	N=195	N=179	p= 0.0104 / 0.0354 ¹
Clinical Resolution	90 (46%)	63 (35%)	(0.95%, 20.97%) ²
Visit 3 (Day 8 + 1 day)	N=197	N=183	p= 0.0023 / 0.0005 ¹
Clinical Resolution	171(87%)	132 (72%)	(6.56%, 22.79%) ²

¹ p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.

² 95% CI for Difference in Percentages; Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 434	Besifloxacin	Moxifloxacin	
Visit 2 (Day 5 ± 1 day)	N=251	N=274	p= 0.6377 / 0.8589 ¹
Clinical Resolution	149 (59%)	165 (60%)	(-9.27%, 7.56%) ²
Visit 3 (Day 8 + 1 day)	N=251	N=274	p= 0.0663 / 0.1985 ¹
Clinical Resolution	223 (89%)	232 (85%)	(-1.66%, 10.01%) ²

¹ p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.

² Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Reviewer's Comments:

Although not necessary to support approval, besifloxacin ophthalmic suspension was superior to its vehicle in the Modified Intent-to-Treat (culture positive) population in Studies #373 and # 433 and was equivalent to the moxifloxacin populations.

Per Protocol (PP) with Last Observation Carried Forward (LOCF)

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N=**	N=**	p=**
Clinical Resolution	()**	()**	
Visit 3 - Day 8 (+ 1 day)	N=42	N=38	CMH* p=0.0965
Clinical Resolution	24 (57%)	16 (42%)	

* Cochran-Mantel-Haenszel

** Data requested from sponsor – submission pending.

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)	N=150	N=132	p= 0.0701 / 0.1879 ¹
Clinical Resolution	71 (47%)	52 (39%)	(-3.71%, 19.59%) ²
Visit 3 (Day 8 + 1 day)	N=130	N=149	p= 0.0023 / 0.0005 ¹
Clinical Resolution	82 (63%)	74 (50%)	(6.56%, 22.79%) ²

¹ p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.

² 95% CI for Difference in Percentages; Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 434	Besifloxacin	Moxifloxacin	
Visit 2 (Day 5 ± 1 day)	N=161	N=180	p= 0.8976 / 0.6578 ¹
Clinical Resolution	95 (59%)	111 (62%)	(-13.10%, 7.77%) ²
Visit 3 (Day 8 + 1 day)	N=150	N=158	p= 0.0342 / 0.1016 ¹
Clinical Resolution	127 (93%)	123 (88%)	(-0.92%, 11.70%) ²

¹ p-Value for Comparison of Treatments; Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.

² Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Reviewer's Comments:

Studies #373 and #433 demonstrate superiority over the drug product's vehicle, and Study #434 demonstrates equivalence to moxifloxacin.

Clinical Microbiology – Bacterial Eradication

Bacterial Eradication is defined as eradication of all pathogens above pathological threshold at baseline.

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (± 1 day) ¹	N=60	N=58	p=0.0691 / 0.0574 ²
Bacterial Eradication	20 (33%)	10(17%)	(0.21%, 31.97%) ³
Visit 3 - Day 8 (+ 1 day) ¹	N=60	N=58	p=0.0003 / 0.0006 ²
Bacterial Eradication	53 (88%)	38 (60%)	(12.11%, 43.87%) ³

1 Missing or Discontinued Subjects imputed as microbial eradication failures.

2 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.

3 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 \pm 1 day) ¹	N=199	N=191	p= <0.0001 / < 0.0001 ²
Bacterial Eradication	182 (92%)	114 (60%)	(23.25%, 40.29%) ³
Visit 3 (Day 8 + 1 day) ¹	N=190	N=191	p= <0.0001 / 0.0001 ²
Bacterial Eradication	176 (84%)	137 (72%)	(8.79%, 24.64%) ³

1 Missing or Discontinued Subjects imputed as microbial eradication failures.

2 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.

3 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Study 434	Besifloxacin	Moxifloxacin	
Visit 2 (Day 5 \pm 1 day) ¹	N=255	N=278	p= <0.0183 / < 0.0544 ²
Bacterial Eradication	241 (95%)	250 (90%)	(-0.01%, 9.17%) ³
Visit 3 (Day 8 + 1 day) ¹	N=255	N=274	p= <0.0748 / 0.3831 ²
Bacterial Eradication	223 (88%)	235 (85%)	(-3.00%, 8.84%) ³

1 Missing or Discontinued Subjects imputed as microbial eradication failures.

2 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.

3 95% CI - Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Reviewer’s comments:

Adequate and well controlled studies (#373, #433 and #434) support the efficacy of besifloxacin hydrochloride ophthalmic suspension for the treatment of bacterial conjunctivitis for the susceptible organisms listed in the Analysis of Secondary Endpoint section.

Analysis of Secondary Endpoints(s)

Secondary endpoints include those organisms treated in the clinical trial to be included in the label.

Organisms that are cultured above the clinically recognized thresholds from an eye with clinical signs and symptoms of bacterial conjunctivitis and treated with the drug product in a clinical trial in 10 or more cases with a $\geq 50\%$ eradication rate are recommended to be included in the labeling. Organisms that are cultured above the clinically recognized thresholds from an eye with clinical signs and symptoms of bacterial conjunctivitis and treated with the drug product in a clinical trial in 5 to 9 cases with a $\geq 80\%$ eradication rate can be considered for inclusion in the labeling with a notation describing the limited number of clinical cases.

Organisms that are cultured in less than 5 infections are not recommended to be included in the label.

Clinical Resolution by cultured organism (cured patients/total patients)

Organism	Besifloxacin - 373	Besifloxacin - 433	Besifloxacin - 434	Vehicle - 373	Vehicle - 433	Moxifloxacin - 434
<i>Abiotrophia defectiva</i>			1/1			
<i>A.calcoaceticus- A.baumannii</i>						
<i>Achromobacter xylosoxidans</i>		2/2		0/1		
<i>Acinetobacter calcoaceticus</i>			1/1			2/2
<i>Acinetobacter Johnson II</i>						
<i>Acinetobacter species</i>				0/1		1/1
<i>Aerococcus viridans</i>			3/3		2/2	4/5
<i>Agrobacterium radiobacter</i>						
<i>Bacillus species</i>		1/1				
<i>Brevibacterium casei</i>			1/1			
<i>Brevibacterium vesicularies</i>						1/1
<i>Brevibacterium species</i>		3/3	2/2		2/3	
CDC coryneform group G	0/2	7/7	6/7		1/2	9/11
CDC coryneform group II		1/1				

Organism	Besifloxacin - 373	Besifloxacin - 433	Besifloxacin - 434	Vehicle - 373	Vehicle - 433	Moxifloxacin - 434
<i>Chryseobacterium indologenes</i>						
<i>Citrobacter koseri</i>						0/1
Coagulase negative staph		1/1		0/1		
<i>Corynebacterium afermentans</i>						1/1
<i>Corynebacterium amycolatum</i>						1/1
<i>Corynebacterium argentoratense</i>				0/1		1/1
<i>Corynebacterium auris</i>			1/1			
<i>Corynebacterium bovis</i>						
<i>Corynebacterium jeikeium</i>		2/2				
<i>Corynebacterium macginleyi</i>		1/1	0/1	0/1		1/3
<i>Corynebacterium minutissimum</i>		1/1	1/1			
<i>Corynebacterium propinquum</i>		1/1		0/1		3/4
<i>Corynebacterium pseudodiphtheriticum</i>	0/1		4/4			0/3
<i>Corynebacterium</i> species			2/2			0/1
<i>Corynebacterium striatum</i>		3/3	1/2			2/3
<i>Corynebacterium urealyticum</i>			1/1		1/1	
<i>Eikenella corrodens</i>			1/1			
<i>Enterobacter cloacae</i>		1/1				
<i>Enterobacter intermedius</i>						
<i>Enterobacter sakazakii</i>	0/1					
<i>Enterococcus faecalis</i>	0/1		0/2			2/2
<i>Escherichia hermannii</i>						
<i>Gemella morbillorum</i>		1/1	0/1			
<i>Gemella</i> species		2/2				
<i>Granulicatella adiacens</i>			2/2			1/2
<i>Haemophilus haemolyticus</i>						
<i>Haemophilus</i>	21/25	56/63	73/81	11/21	48/66	82/88

Organism	Besifloxacin - 373	Besifloxacin - 433	Besifloxacin - 434	Vehicle - 373	Vehicle - 433	Moxifloxacin - 434
<i>influenzae</i>						
<i>Haemophilus parainfluenzae</i>		1/1		1/2		2/2
<i>Klebsiella denitrificans</i>			1/1			
<i>Klebsiella oxytoca</i>		1/2				
<i>Klebsiella ozarnae</i>			0/1			
<i>Klebsiella pneumoniae</i>						
<i>Kocuria kristine</i>			1/1		1/1	
<i>Leminorella species</i>						1/1
Micrococcus species			1/1		0/1	
<i>Moraxella catarrhalis</i>		1/1	2/2	0/1	3/3	4/5
<i>Moraxella lacunata</i>		1/1	4/4		2/3	1/1
<i>Moraxella nonliquefaciens</i>						1/1
<i>Moraxella species</i>						1/1
<i>Morganella morganii</i>						1/1
<i>Neisseria gonorrhoeae</i>			2/2			
<i>Neisseria meningitidis</i>		1/1	1/1	0/1		
<i>Neisseria mucosa</i>						
<i>Neisseria sicca</i>			1/1			
<i>Neisseria subflava</i>						1/1
<i>Ochrobactrum anthropi</i>						
<i>Pasteurella multocida</i>					0/1	1/3
<i>Proteus mirabilis</i>			1/1			2/4
<i>Providencia rettgeri</i>						
<i>Pseudomonas aeruginosa</i>		2/2	1/2		1/1	2/3
<i>Pseudomonas fluoresceins</i>						1/1
Rhodococcus species						
<i>Rothia mucilaginosa</i>		1/1				
<i>Serratia marcescens</i>	0/1	2/2		0/1		5/5
<i>Serratia species</i>						
<i>Staphylococcus aureus</i>	4/6	17/23	50/58	2/9	23/32	41/57
<i>Staphylococcus auricularis</i>						
<i>Staphylococcus capitis</i>	0/1		1/3			1/1

Organism	Besifloxacin - 373	Besifloxacin - 433	Besifloxacin - 434	Vehicle - 373	Vehicle - 433	Moxifloxacin - 434
<i>Staphylococcus caprae</i>		1/1	1/1		1/1	1/1
<i>Staphylococcus chromogenes</i>						1/1
<i>Staphylococcus epidermidis</i>	1/2	13/16	21/29	0/4	16/18	34/41
<i>Staphylococcus haemolyticus</i>			1/1		1/1	0/1
<i>Staphylococcus hominis</i>		2/2	3/4		1/2	0/1
<i>Staphylococcus intermedius</i>	0/1					
<i>Staphylococcus lugdunensis</i>		1/1	5/5			1/2
<i>Staphylococcus simulans</i>						
<i>Staphylococcus warneri</i>		1/1	2/2		0/1	1/1
<i>Staphylococcus xylosum</i>		1/1				0/1
<i>Stenotrophomonas maltophilia</i>	0/1	1/1	3/3	0/1		3/3
<i>Stomatococcus mucilaginosus</i>						
<i>Streptococcus agalactiae</i>				0/1		
<i>Streptococcus anginosus</i>			1/1			1/1
<i>Streptococcus anginosus group</i>			1/1			
<i>Streptococcus dysgalactiae</i>		1/1			1/1	
<i>Streptococcus intermedius</i>						
<i>Streptococcus milleri group</i>					1/1	
<i>Streptococcus mitis</i>		6/6	3/3	0/1	2/4	3/5
<i>Streptococcus mitis group</i>	1/1	7/9	10/11		9/10	14/14
<i>Streptococcus oralis</i>	0/2	2/3	5/6	1/1	0/1	4/4
<i>Streptococcus parasanguinis</i>			1/1			1/1
<i>Streptococcus pneumoniae</i>	15/24	60/74	51/58	5/14	45/66	53/64
<i>Streptococcus pyogenes</i>		0/1			1/2	2/2
<i>Streptococcus salivarius</i>		3/3	1/2		2/2	2/2
<i>Streptococcus sanguis</i>		1/2	1/2			
<i>Streptococcus thermophilus</i>			1/1			

Organism	Besifloxacin - 373	Besifloxacin - 433	Besifloxacin - 434	Vehicle - 373	Vehicle - 433	Moxifloxacin - 434
<i>Streptococcus</i> species		1/2	3/3		2/4	2/4
<i>Streptococcus</i> <i>viridans</i>					1/1	

Reviewer’s comments:

Efficacy was demonstrated in patients with cultures positive for:

Gram-positive microorganisms: CDC coryneform group G; *Corynebacterium pseudodiphtheriticum**; *Corynebacterium striatum**; *Staphylococcus aureus*; *Staphylococcus epidermidis*; *Staphylococcus hominis**; *Staphylococcus lugdunensis**; *Streptococcus mitis* group; *Streptococcus oralis*; *Streptococcus pneumoniae*; *Streptococcus salivarius**, and

Gram-negative microorganisms: *Haemophilus influenzae*; *Moraxella lacunata**

*Efficacy of this organism was studied in fewer than 10 infections.

Subpopulations

Pediatric Results

Clinical Resolution Age 2 and less

	Besifloxacin	Besi Vehicle	
Visit 2	N= 19	N= 14	p= <0.0477 / < 0.4824 ¹
Clinical Resolution	10 (53%)	5 (36%)	(-18.85%, 52.69%) ²
Visit 3 - Day 8 (+ 1 day)	N=19	N=14	p= <0.0792 / 0.0616 ¹
Clinical Resolution	18 (95%)	9 (64%)	(2.74%, 58.16%) ²

1 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.

2 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Clinical Resolution Ages 2 - 19

	Besifloxacin	Besi Vehicle	
Visit 2	N= 123	N= 115	p= <0.1397 / < 0.1526 ¹
Clinical Resolution	61 (50%)	46 (40%)	(-3.12%, 22.31%) ²
Visit 3 - Day 8 (+ 1 day)	N=123	N=115	p= <0.0693 / 0.0197 ¹
Clinical Resolution	103 (84%)	81 (70%)	(2.60%, 24.01%) ²

1 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.

2 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Microbial Eradication Age 2 and less

	Besifloxacin	Besi Vehicle	
Visit 2	N= 19	N= 14	p= <0.0267 / < 0.0152 ¹
Microbial Eradication	14 (74%)	4 (28%)	(9.34%, 80.88%) ²
Visit 3 - Day 8 (+ 1 day)	N=19	N=14	p= <0.03853 / 0.4421 ¹
Microbial Eradication	15 (79%)	9 (64%)	(-17.33%, 46.65%) ²

1 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.

2 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Microbial Eradication Ages 2 - 19

	Besifloxacin	Besi Vehicle	
Visit 2	N= 123	N= 115	p= <0.0001 / < 0.0001 ¹
Microbial Eradication	109 (89%)	68 (59%)	(18.33%, 40.64%) ²
Visit 3 - Day 8 (+ 1 day)	N=123	N=115	p= <0.0191 / 0.0059 ¹
Microbial Eradication	103 (84%)	78 (68%)	(5.01%, 26.82%) ²

1 p-Values from the Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, respectively.

2 95% CI - Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Reviewer's comments:

Adequate and well controlled studies (Studies #373, #433 and #434) included a sufficient number of pediatric subjects to support the efficacy of besifloxacin hydrochloride ophthalmic suspension for the treatment of bacterial conjunctivitis for ages one and older.

Integrated Review of Safety

The three clinical studies (Studies #373, #433 and #434) were used to establish the safety of the drug product. Overall, the safety population included 1,192 subjects in the besifloxacin group, 616 subjects in the besifloxacin vehicle group and 579 subjects in the moxifloxacin group

Deaths

No deaths occurred during the course of the Studies.

Nonfatal Serious Adverse Events

There were four serious adverse events reported. Three subjects had received the study drug and one subject required hospitalization for dehydration, another required hospitalization for pneumonia and another for congestive heart failure. One subject from the Moxifloxacin treatment group was hospitalized for an acute viral illness.

Overall Listing of Serious Adverse Events

There were no other serious adverse events reported.

Adverse Events That Led To Discontinuation from the Studies

Study	Site ID	Subj. ID	Study eye	Treatment Group	Reason for Withdrawal	AE description
373	33	026	OD	Vehicle	AE	preseptal cellulitis OU
433	664475	0812	OS	Vehicle	AE	otitis media, conjunctivitis OD
	683540	0722	OD	Vehicle	AE	conjunctival edema and prominent vesicles OS
	685455	0597	OD	Besifloxacin	AE	worsening conjunctivitis OD
	690450	0279	OS	Vehicle	AE	earache
	697443	0933	OD	Besifloxacin	AE	dermatitis on face, legs, arms
	704436	0338	OD	Vehicle	AE	corneal infiltrates OS
	715426	0637	OS	Besifloxacin	AE	bilateral otitis media
	725416	0652	OD	Besifloxacin	AE	bilateral otitis media, fever
	726415	0322	OS	Vehicle	AE	worsening conjunctivitis OS
599539	1243	OD	Vehicle	AE	pneumonia	
434	252853	0251	OD	Besifloxacin	AE	worsening conjunctivitis OD, conjunctivitis OS
	442665	0849	OD	Besifloxacin	AE	strep throat, conjunctivitis OS
	497614	0286	OD	Moxifloxacin	AE	respiratory infection
	665474	0742	OD	Moxifloxacin	AE	corneal abrasion OU
	665474	0874	OD	Besifloxacin	AE	episcleritis OD
	673466	0220	OS	Besifloxacin	AE	keratitis OS
	680459	0902	OD	Besifloxacin	AE	herpes simplex virus OD
	711585	0032	OS	Besifloxacin	AE	congestive heart failure
	711585	0954	OS	Besifloxacin	AE	worsening conjunctivitis OS
	711585	0955	OS	Besifloxacin	AE	headache, sore throat, body aches
	728413	0927	OD	Besifloxacin	AE	photophobia OU
	750393	1229	OD	Besifloxacin	AE	fever, leucocytosis
	760384	1165	OD	Besifloxacin	AE	exacerbation of bacterial conjunctivitis and eye pain OD
	762382	0065	OD	Moxifloxacin	AE	eye pain, lid swelling, increased tearing, white spot OD
	842556	0117	OD	Moxifloxacin	AE	iritis, VA decreased OD
868286	2015	OD	Moxifloxacin	AE	allergy to study drug-OU	

**Adverse Events Reported - Safety Population
Studies #373, #433 and #434**

	Besifloxacin (N=1192)	Vehicle (N=616)	Moxifloxacin (N=579)
Total Number of Ocular Events	191	146	81
Number of Patients with at Least One AE	139 (12%)	101 (16%)	54 (9%)
Eye irritation	17 (1.4%)	18(2.9%)	8 (1.4%)
Eye pain	22 (1.8%)	11 (1.8%)	7 (1.2%)
Worsening bacterial conjunctivitis	7 (0.6%)	9 (1.5%)	2 (0.3%)
Conjunctivitis	14 (1.2%)	15 (2.4%)	5 (0.9%)
Eye pruritus	13 (1.1%)	10 (1.6%)	2 (0.3%)
Vision blurred	25 (2.1%)	24 (3.9%)	3 (0.5%)
Eyelid oedema	5 (0.4%)	3 (0.5%)	5 (0.9%)
Eye discharge	3 (0.3%)	4 (0.6%)	3 (0.5%)
Conjunctival haemorrhage	4 (0.8%)	3 (0.5%)	3 (0.5%)
Conjunctival hyperaemia	6 (0.5%)	2 (0.3%)	0
Conjunctival oedema	6 (0.5%)	2 (0.3%)	1 (0.2%)
Corneal infiltrates	6 (0.5%)	1 (0.2%)	2 (0.3%)
Punctate keratitis	4 (0.3%)	2 (0.3%)	3 (0.5%)
Visual acuity reduced	3 (0.3%)	3 (0.5%)	2 (0.3%)
Conjunctivitis viral	6 (0.5%)	0	1 (0.2%)
Dry eye	3 (0.3%)	1 (0.2%)	3 (0.5%)
Eyelid margin crusting	3 (0.3%)	3 (0.5%)	1 (0.2%)
Limbal hyperemia	2 (0.2%)	2 (0.3%)	3 (0.5%)
Ocular hyperemia	3 (0.3%)	3 (0.5%)	1 (0.2%)
Conjunctival disorder	2 (0.2%)	1 (0.2%)	3 (0.5%)
Lacrimation increased	1 (0.1%)	3 (0.5%)	2 (0.3%)
Eye inflammation	1 (0.1%)	2 (0.3%)	2 (0.3%)
Foreign body sensation	3 (0.3%)	1 (0.2%)	0
Abnormal sensation in eye	0	3 (0.5%)	0
Conjunctival follicles	1 (0.1%)	0	2 (0.3%)
Erythema of eyelid	1 (0.1%)	1 (0.2%)	1 (0.2%)
Blepharitis	1 (0.2%)	1 (0.2%)	0
Corneal erosion	1 (0.1%)	1 (0.2%)	0
Eye infection	0	1 (0.2%)	1 (0.2%)
Eye swelling	0	2 (0.3%)	0
Eyelid disorder	1 (0.1%)	1 (0.1%)	0
Keratitis	1 (0.1%)	0	1 (0.2%)
Keratoconjunctivitis sicca	2 (0.2%)	0	0
Photophobia	1 (0.1%)	0	1 (0.2%)
Visual disturbance	2 (0.2%)	0	0
Adenoviral conjunctivitis	0	1 (0.2%)	0
Altered visual depth perception	1 (0.1%)	0	0
Anterior chamber inflammation	1 (0.1%)	0	0
Blepharitis allergic	0	1 (0.2%)	0
Blepharospasm	1 (0.1%)	0	0
Chalazion	0	1 (0.2%)	0
Conjunctival cyst	0	1 (0.2%)	0
Conjunctivitis allergic	1 (0.1%)	0	0
Corneal abrasion	0	0	1 (0.2%)
Corneal disorder	0	0	1 (0.2%)

	Besifloxacin (N=1192)	Vehicle (N=616)	Moxifloxacin (N=579)
Corneal opacity	1 (0.1%)	0	0
Episcleritis	1 (0.1%)	0	0
Eye disorder	1 (0.1%)	0	0
Eye movement disorder	0	1 (0.2%)	0
Eyelid irritation	0	0	1 (0.2%)
Herpes simplex ophthalmic	1 (0.1%)	0	0
Hordeolum	1 (0.1%)	0	0
Iritis	0	0	1 (0.2%)
Ocular discomfort	0	1 (0.2%)	0
Periorbital cellulitis	0	1 (0.2%)	0
Photopsia	1 (0.1%)	0	0
Pinguecula	0	0	1 (0.2%)
Vitreous floaters	0	1 (0.2%)	0
Drug hypersensitivity	0	0	1 (0.2%)
Instillation site irritation	0	1 (0.2%)	0
Instillation site pain	1 (0.1%)	0	0
Investigations- corneal staining	2 (0.2%)	1 (0.2%)	2 (0.3%)
Dermatitis contact	0	0	2 (0.3%)
Dry skin	1 (0.1%)	0	0
Skin ulcer	0	0	1 (0.2%)
Total Number of Systemic Events	107	64	45
Number of Patients with at Least One AE	75 (6%)	48 (8%)	31 (5%)
Lymphadenopathy	2 (0.2%)	0	0
Anaemia	1 (0.1%)	0	0
Leukocytosis	1 (0.1%)	0	0
Cardiac failure congestive	1 (0.1%)	0	0
Ear pain	1 (0.1%)	2 (0.3%)	0
Hypoacusis	1 (0.1%)	0	1 (0.2%)
Tinnitus	1 (0.1%)	0	0
Vertigo	1 (0.1%)	0	0
Eye pruritis	1 (0.1%)	0	0
Nausea	1 (0.1%)	1 (0.2%)	2 (0.3%)
Diarrhoea	1 (0.1%)	2 (0.3%)	0
Vomiting	1 (0.1%)	1 (0.2%)	1 (0.2%)
Abdominal pain upper	0	2 (0.3%)	0
Dysgeusia	1 (0.1%)	0	0
Glossodynia	0	0	1 (0.2%)
Tongue blistering	1 (0.1%)	0	0
Toothache	0	0	1 (0.2%)
Pyrexia	6 (0.5%)	4 (0.6%)	1 (0.2%)
Fatigue	1 (0.1%)	1 (0.2%)	0
Influenza like illness	1 (0.1%)	0	0
Pain	1 (0.1%)	0	1 (0.2%)
Seasonal allergy	1 (0.1%)	0	0
Upper respiratory tract infection	2 (0.2%)	2 (0.3%)	4 (0.7%)
Pharyngitis streptococcal	3 (0.3%)	3 (0.5%)	1 (0.2%)
Nasopharyngitis	2 (0.2%)	2 (0.3%)	2 (0.3%)
Otitis media	4 (0.3%)	1 (0.2%)	0

	Besifloxacin (N=1192)	Vehicle (N=616)	Moxifloxacin (N=579)
Ear infection	2 (0.2%)	2 (0.3%)	1 (0.2%)
Bronchitis	2 (0.2%)	1 (0.2%)	1 (0.2%)
Sinusitis	3 (0.3%)	0	1 (0.2%)
Pneumonia	1 (0.1%)	1 (0.2%)	0
Viral upper respiratory tract infection	2 (0.2%)	0	0
Gastroenteritis	1 (0.1%)	0	0
Herpes zoster	0	0	1 (0.2%)
Urinary tract infection	1 (0.1%)	0	0
Viral infection	0	0	1 (0.2%)
Excoriation	1 (0.1%)	0	0
Head injury	1 (0.1%)	0	0
Sunburn	1 (0.1%)	0	0
Anorexia	1 (0.1%)	0	0
Decreased appetite	0	0	1 (0.2%)
Back pain	1 (0.1%)	0	0
Myalgia	0	0	1 (0.2%)
Pain in extremity	1 (0.1%)	0	0
Headache	21 (1.8%)	11 (1.8%)	9 (1.6%)
Dizziness	1 (0.1%)	0	1 (0.2%)
Loss of consciousness	1 (0.1%)	0	0
Migraine	0	1 (0.2%)	0
Sinus headache	1 (0.1%)	0	0
Somnolence	1 (0.1%)	0	0
Anxiety	1 (0.1%)	0	1(0.2%)
Depression	2 (0.2%)	0	0
Insomnia	0	1 (0.2%)	0
Pharyngolaryngeal pain	8 (0.7%)	5 (0.8%)	3 (0.5%)
Cough	4 (0.3%)	4 (0.6%)	1 (0.2%)
Asthma	2 (0.2%)	1 (0.2%)	1 (0.2%)
Nasal congestion	2 (0.2%)	1 (0.2%)	1 (0.2%)
Respiratory tract congestion	2 (0.2%)	0	1 (0.2%)
Epistaxis	1 (0.1%)	1 (0.2%)	0
Rhinorrhoea	1 (0.1%)	1 (0.2%)	0
Dyspnoea	0	1 (0.2%)	0
Nasal dryness	1 (0.1%)	0	1 (0.2%)
Rhinitis allergic	1 (0.1%)	0	0
Wheezing	0	1 (0.2%)	0
Rosacea	0	1 (0.2%)	1 (0.2%)
Blister	0	1 (0.2%)	0
Dermatitis allergic	1 (0.1%)	0	0
Dermatitis contact	0	1 (0.2%)	0
Eyelid pain	0	1 (0.2%)	0
Skin hyperpigmentation	0	0	1 (0.2%)
Swelling face	1 (0.1%)	0	0
Urticaria	1 (0.1%)	0	0

Reviewer's Comments:

There were relatively few reported adverse experiences (individual events all less than 2% except for blurred vision occurring in 2.1%). Other frequently reported adverse experiences were eye pain, 1.8%; eye irritation, 1.4%; conjunctivitis bacterial, 1.2%; and eye pruritis, 1.1%.

Laboratory Findings/Special Safety Studies

There were no clinically significant differences in fasting blood chemistry, hematology, and urinalysis reported in any treatment groups. Changes in test results were similar in the besifloxacin ophthalmic suspension treatment groups and their vehicle groups.

There were no clinically significant differences in heart rate, systolic and diastolic blood pressure between besifloxacin ophthalmic suspension and its vehicle control.

There were no significant differences in EKG findings between the vehicle and the besifloxacin ophthalmic suspension groups. No clinically significant abnormalities in EKG were found in besifloxacin ophthalmic suspension treated subjects.

Special Safety Studies

Adverse Events Age 2 and less Safety Population

	Besifloxacin	Besi Vehicle	Moxifloxacin	p-value
	N= 46	N= 21	N= 14	
Total Number of Adverse Events	0	2	4	
Subjects with at Least One Adverse Event	0	2 (9.5%)	2 (14%)	p= 0.095 ¹

¹ p-Values based on Fischer's Exact test, comparing Besifloxacin and Besi Vehicle.

Adverse Events Ages 2 - 19 Safety Population

	Besifloxacin	Besi Vehicle	Moxifloxacin	p-value
	N= 403	N= 237	N= 170	
Total Number of Adverse Events	45	27	5	
Subjects with at Least One Adverse Event	37 (9%)	23 (10%)	4 (2%)	p= 0.8885 ¹

¹ p-Values based on Fischer's Exact test, comparing Besifloxacin and Besi Vehicle.

Reviewer's comments:

Adequate and well controlled studies (Studies #373, #433 and #434) included a sufficient number of pediatric subjects to support the safety of besifloxacin hydrochloride ophthalmic suspension for the treatment of bacterial conjunctivitis for ages one and older.

Post-marketing Experience

There is no post-marketing experience with besifloxacin hydrochloride ophthalmic suspension. This is a new chemical entity and has not been marketed anywhere in the world.

Potential Questions for the Advisory Committee

- 1) Do you think besifloxacin hydrochloride ophthalmic suspension should be approved for the treatment of bacterial conjunctivitis?
- 2) If not, what additional studies should be performed?
- 3) Do you have any suggestions concerning the labeling of the product?