CLINICAL REVIEW

Application Type	NDA
Submission Number	22-308
Submission Code	N-000
Letter Date	May 30, 2008
Stamp Date	June 2, 2008
PDUFA Goal Date	April 2, 2009
Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	February 5, 2009
Established Name	Besifloxacin hydrochloride ophthalmic suspension, 0.6%
(Proposed) Trade Name	Besivance™
Therapeutic Class	Ophthalmic fluoroquinolone
Applicant	Bausch & Lomb Incorporated
Priority Designation	S
Formulation	Ophthalmic suspension, 0.6%
Dosing Regimen	One drop in the affected eye (s) three times daily for seven days
Indication	Treatment of bacterial conjunctivitis
Intended Population	Patients ages 1 and older with bacterial conjunctivitis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended from a clinical prospective that NDA 22-308, Besivance (besifloxacin ophthalmic suspension) be approved for the treatment of bacterial conjunctivitis with labeling revisions listed in this review.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Besivance, when dosed three times a day for seven days, is superior to its vehicle and equivalent to Moxifloxacin (moxifloxacin hydrochloride ophthalmic solution) in the treatment of bacterial conjunctivitis.

1.2 Risk Benefit Assessment

Studies #373 and #433 demonstrate superiority over the drug product's vehicle, and Study #434 demonstrates equivalence to moxifloxacin in the primary efficacy endpoint of clinical resolution; these adequate and well controlled studies support the efficacy of besifloxacin hydrochloride ophthalmic suspension for the treatment of bacterial conjunctivitis for the susceptible organisms listed in the final labeling. Pooled adverse event data for these trials showed 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%.

1.3 Recommendations for Postmarketing Risk Management Activities

There are no recommended Phase 4 commitments.

1.4 Recommendations for other Post Marketing Study Commitments

There are no recommended Phase 4 commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Name:	Besivance (besifloxacin ophthalmic suspension)
Chemical Class:	New Chemical Entity
Therapeutic Class:	Ophthalmic fluoroquinolone antibiotic

Indication:	Besivance™ is a topical ophthalmic preparation of a fluoroquinolone anti-infective indicated for the treatment of bacterial conjunctivitis caused by the following organisms: Aerobic and facultative 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** Aerobic and facultative Gram-negative microorganisms: *Haemophilus influenzae; Moraxella lacunata** *Efficacy for this organism was studied in fewer than 10 infections.
Dosing Regimen:	One drop in the affected eye(s) three times a day for seven days

2.2 Tables of Currently Available Treatments for Proposed Indications

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, and moxifloxacin ophthalmic solution.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, besifloxacin hydrochloride, is a fluoroquinolone anti-infective and is a new chemical entity developed for ophthalmic use.

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

An End of Phase 1 Meeting was held on May 25, 2004, and an End of Phase 2 Meeting was held on December 6, 2005. A Pre-NDA meeting was held on June 6, 2007. At the end of each of the meetings, the Agency provided general guidance; there were no scientific disagreements.

On December 5, 2008 the Dermatologic and Ophthalmic Drug Advisory Committee reviewed NDA 22-308. The Advisory recommended approval of besifloxacin hydrochloride ophthalmic suspension, 0.6%.

2.6 Other Relevant Background Information

Besifloxacin is a new chemical entity and is not approved for marketing anywhere in the world.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested. Bausch & Lomb Incorporated terminated the two sites, Zosa and Asbell, early in the trials. If the data from Zosa and Asbell are excluded, there is no significant change in either the safety or efficacy conclusions for this NDA. An audit of the analytical and clinical portions of Studies 373, 433, and 434 noted minor regulatory violations in three of the four sites selected for audit because of the size of enrollment; these sites inspected by DSI (Rigel, Heller, McGriff, and Kanengiser) have violations which do not significantly affect the overall reliability of safety and efficacy data. See the original DSI review dated February 23, 2009.

3.2 Compliance with Good Clinical Practices

The is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

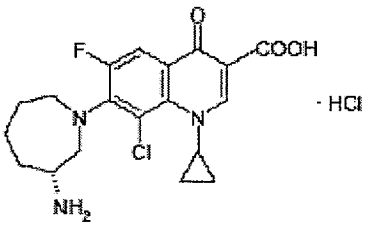
3.3 Financial Disclosures

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided by [redacted] for the covered clinical studies submitted in this application: 373, 433, and 434. b(4)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Besivance™ (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.



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

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

Besifloxacin hydrochloride is a white to pale yellowish-white powder. Each mL of Besivance™ contains 6.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base.

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.

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

Composition of Besifloxacin HCl Ophthalmic Suspension 0.6% w/w as Base

	W01N	
Scale	12 L	
Ingredient	% w/w	
Besifloxacin HCl (as free base)	[redacted] (0.6)	b(4)
Polycarbophil, USP	[redacted]	
Edetate Disodium Dihydrate, USP	[redacted]	b(4)
Sodium Chloride, USP	[redacted]	
Mannitol, USP	[redacted]	
Poloxamer 407, NF	[redacted]	
Benzalkonium Chloride, NF	0.10	
Sodium Hydroxide [redacted]	[redacted]	b(4)
Sterile Water [redacted] USP	[redacted]	

4.2 Clinical Microbiology

Besifloxacin is an 8-chloro fluoroquinolone with a N-1 cyclopropyl group. The compound has activity against aerobic, facultative, and anaerobic 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. Besifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs).

The mechanism of action of fluoroquinolones, including besifloxacin, is different from that of aminoglycoside, macrolide, tetracycline, β-lactam, sulfonamide, and cyclic peptide antibiotics. Therefore, besifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to besifloxacin. *In vitro* studies demonstrated cross-resistance between besifloxacin and some other fluoroquinolones. *In vitro* resistance to besifloxacin develops via multiple-step mutations and occurs at a general frequency of $< 3.3 \times 10^{-10}$ for *Staphylococcus aureus* and $< 7 \times 10^{-10}$ for *Streptococcus pneumoniae*.

Besifloxacin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in conjunctival infections treated in clinical trials as listed below:

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**

Aerobic and facultative Gram-negative microorganisms:

*Haemophilus influenzae; Moraxella lacunata**

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

In vitro data are available for other microorganisms, but their clinical significance in ophthalmic infections is unknown. Because systemic breakpoints for besifloxacin are not available to evaluate susceptibility of clinical isolates, a correlation between *in vitro* susceptibility data and ophthalmological efficacy for other microorganisms has not been established.

4.3 Preclinical Pharmacology/Toxicology

The ocular tolerability of besifloxacin ophthalmic suspension was shown to be favorable in rabbits and dogs after four times daily topical repeat dosing for 28 days.

Minimal effects were observed following oral systemic administration for 28 days of high doses of besifloxacin (up to 500 mg/kg/day). Minor urinary changes (increased urinary proteins and decreased pH) and decreased heart weight at 500 mg/kg were the primary effects in the rat while emesis, increased salivation, and transient facial swelling coupled with pupillary dilation were

observed in the dog. No bones or joints alterations were observed. Systemic NOAELs following repeat oral dosing were 500 mg/kg and 5 mg/kg in rats and dogs, respectively. The NOAEL for increased QT interval duration was 10 mg/kg in dogs. Although potential phototoxic effects were observed after oral dosing in mice, no photo-irritant effects were seen when besifloxacin was administered cutaneously to guinea pigs. Compared with the daily human dose, the calculated safety margin for all endpoints is greater than 150, indicating an extremely low risk to humans.

Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed.

No *in vitro* mutagenic activity of besifloxacin was observed in an Ames test (up to 3.33 µg/plate) on the recommended bacterial tester strains (i.e., *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA). There were some indications of positive genotoxic responses, likely related to topoisomerase inhibition, in other Ames tests, with and without solar simulated light, using specific bacterial tester strains (i.e. *Salmonella typhimurium* TA102, TA1537 and *Escherichia coli* WP2(pKM101)), and in an *in vitro* chromosomal aberration test in CHO cells. *In vivo*, besifloxacin racemate was devoid of clastogenic potential in a mouse micronucleus assay by the intraperitoneal route (up to 500 mg/kg) however besifloxacin was positive in an *in vivo* mouse micronucleus assay by the oral route. The NOAEL was 1,000 mg/kg associated with a systemic exposure of ~4 µg/mL indicating a 10,000 safety factor compared with human systemic exposure. Besifloxacin induced no primary DNA damage in hepatocytes cultured from rats given the test compound up to 2,000 mg/kg by the oral route. There was no additional genotoxic response due to the presence of solar simulated light in the Ames assay, demonstrating the absence of photomutagenic potential of besifloxacin in bacteria.

In a fertility and early embryonic development oral study in rats, the NOAEL was 100 mg/kg/day for maternal toxicity, based on changes in appearance and behavior and decreased bodyweight at 500 mg/kg/day. The NOAEL for reproductive performance and fertility in rats was 500 mg/kg/day which is approximately 16,000 times the highest recommended total daily human ophthalmic dose.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Besifloxacin is an 8-chloro fluoroquinolone with a N-1 cyclopropyl group. The compound has activity against aerobic, facultative, and anaerobic Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV.

4.4.2 Pharmacodynamics

Refer to the Pharmacokinetics section (4.4.3) and the Pharm/Tox review.

4.4.3 Pharmacokinetics

Plasma concentrations of besifloxacin were measured in adult male and female patients with suspected bacterial conjunctivitis who received Besivance™ 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 received a single drop of Besivance™. Following a single administration, the mean besifloxacin C_{max} in tear samples was 610 µg/g and the estimated total exposure (AUC 0-24h) was 1,232 µg*h/g. The mean besifloxacin concentration observed in samples collected 24 hours after a single administration was 1.6 µg/g.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Type of Study	Study #	Study Design / Type of Control	Study Objective(s)	Products: Dosing; Route of Administration	Number of Subjects	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 resolution and eradication of baseline bacterial infection at Day 8
Safety and Efficacy	433	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	957 (473-study drug, 484 vehicle) / 874 (442 study drug, 432 vehicle) completed	Clinical resolution and eradication of baseline bacterial infection at Day 5
Safety	434	Multicenter	Evaluate	Besifloxacin	1161	Clinical resolution

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

5.2 Review Strategy

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 Besivance (besifloxacin hydrochloride ophthalmic suspension, 0.6%) to Moxifloxacin (moxifloxacin hydrochloride ophthalmic solution 0.5%).

5.3 Discussion of Individual Studies

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 day)		X	X			X	X[3]	X
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 Events[1]	X	X	X
Concomitant Medications	X	X	X
Dispense Drugs[2]	X		
Instill Drug at Site	X	X	
Weigh Medication	X	X	X

Bottle(s)			
Study Exit[3]			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 intill 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

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
697443	De Leon, Jose, M.D.	Paramount, CA	25/14/13	25/5/3
231868	Donshik, Peter, M.D.	Bloomfield, CT	1/1/1	2/0/0
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	0	0
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

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Vehicle
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
690450	Yee, Richard, M.D.	Houston, TX	7/0/0	6/1/0
691449	Zosa, Noli, M.D.	Pico Riveria, 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 Moxifloxacin 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 Moxifloxacin in the treatment of bacterial conjunctivitis. (Enrolled/Culture Positive/Cure)

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Moxifloxacin
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

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Moxifloxacin
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
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	2/1/0	2/1/1
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

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Moxifloxacin
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
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, Barry, 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

Site #	Investigator	Study Location	Besifloxacin hydrochloride ophthalmic suspension, 0.6%	Moxifloxacin
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

6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

The applicant conducted three adequate and well controlled clinical trials: Studies 373 and 433 were superiority trials, and Study 434 was an equivalence trial. These three clinical studies were used to establish the efficacy of the drug product.

Bacterial conjunctivitis is generally a self limited disease with a usual course of 7-14 days. The goal of therapy is to reduce the duration of the illness and minimize the chances of infecting other individuals. Efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials of at least 7 days in duration. Independence refers to different investigators and different geographic locations between the trials. Demonstration of efficacy is recommended to include evidence of statistical significance and clinical relevance. Clinical relevance or a clinical cure is recommended to be defined as the resolution of signs and symptoms (i.e. a score of 0, normal conjunctiva and no discharge) for the infected patients who meet the inclusion criteria of the protocol.

The following are recommended demonstrations of efficacy:
1. Statistically significant superiority in replicated studies to the product's vehicle in the cure of the signs and symptoms of bacterial conjunctivitis in clinically infected patients who meet the inclusion criteria.

2. An alternative approach for drug substances which have already demonstrated efficacy in another anti-infective indication is to show superiority to vehicle in one trial and equivalence to tobramycin or one of the approved fluoroquinolones dosed qid in another trial. Equivalence is defined as the having a two sided 95% confidence interval for the difference in cure rates of less than 6%.

Additionally, in trials which include the test product's vehicle in one arm, it is recommended that the cure rate of the vehicle should not be numerically superior to the cure rate of the test product for the Intent-to-Treat population.

6.1.2 Demographics

Studies 373, 433 and 434
Safety population

	Besifloxacin (N=1192)	**Besi Vehicle (N= 616)**	**Moxifloxacin (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%)	36 (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%)

6.1.3 Patient Disposition

There were a significant number of patients treated in all age groups.

6.1.4 Analysis of Primary Endpoint(s) – Clinical Resolution

Clinical Resolution is defined as absence of all three clinical signs: ocular discharge, bulbar conjunctival injection, and palpebral conjunctival injection.

For Study #373 the Safety population was the same as the ITT, Intent To Treat, for Studies #433 and #434.

The safety 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.

For Study #373 the Intent To Treat , ITT population, was the same as the mITT, modified Intent To Treat, for Studies #433 and #434.

All subjects who were randomized to treatment who received at least one drop of the study medication and had baseline cultures indicating pathogenic bacterial levels were included in the intent-to-treat population.

The Per Protocol population, PP, was the same definition for all three: Studies #373, #433 and #434.

Those intent-to-treat subjects who did not have a major protocol violation were included in the per-protocol population. 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.

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

(For Study # 373 Safety Population is the same as ITT for Studies # 433 and #434)

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N= 136	N= 130	p= 0.0905[1]
Clinical Resolution	33 (24%)	20 (16 %)	(-0.0063, 0.1851)[2]
Visit 3 - Day 8 (+ 1 day)	N=136	N=130	p=0.0013[3]
Clinical Resolution	89 (65%)	59 (45%)	(0.0835, 0.3177)[2]

1 Pearson Chi-square Statistic 3.29, exact p-value
2 95% CI difference in proportions
3 Pearson Chi-square Statistic 10.83, exact p-value

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=582	N=579	p= 0.9682 / 0.8594[1]
Clinical Resolution	321 (55%)	323 (56%)	(-6.35%, 5.09%)[2]
Visit 3 (Day 8 + 1 day)	N=582	N=579	p= <0.8007 / >0.9377[1]
Clinical Resolution	488 (85%)	486 (85%)	(-4.06%, 4.58%)[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
(For Study # 373 Intent To Treat is the same as modified ITT for Studies # 433 and #434)

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N=60	N=56	p=0.2434[1]
Clinical Resolution	14 (23%)	8 (14%)	(-0.0504, 0.2314)[2]
Visit 3 - Day 8 (+ 1 day)	N=60	N=56	p=0.0058[3]
Clinical Resolution	37 (62%)	20 (36%)	(0.0838, 0.4353)[2]

1 Pearson Chi-square Statistic 1.54, exact p-value
2 95% CI difference in proportions
3 Pearson Chi-square Statistic 7.81, exact p-value

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)
(PP population criteria same for all three studies - #373, #433 and #434)

Study 373	Besifloxacin	Vehicle	
Visit 2 - Day 4 (±1 day)	N= 42	N= 38	p=0.02869[1]
Clinical Resolution	11 (26%)	6 (16%)	(-0.724%, 0.2869%)[2]
Visit 3 - Day 8 (+ 1 day)	N=42	N=38	p=0.2629[3]
Clinical Resolution	24 (57%)	16 (42%)	(-0.0665, 0.3673)[2]

1 Pearson Chi-square Statistic 1.29, exact p-value
2 95% CI difference in proportions
3 Pearson Chi-square Statistic 1.80, exact p-value

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)	N=151	N=133	p= 0.0701 / 0.1879[1]
Clinical Resolution	71 (47%)	52 (39%)	(-3.71%, 19.59%)[2]
Visit 3 (Day 8 + 1 day)	N=151	N=133	p= 0.2649 / 0.0837[1]
Clinical Resolution	131 (87%)	105 (79%)	(-0.96%, 16.58%)[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=161	N=180	p= 0.0342 / 0.1016[1]
Clinical Resolution	150 (93%)	158 (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.

6.1.5 Analysis of Secondary Endpoints(s)

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

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

Organism	Vehicle - 373	Besifloxacin - 373	Vehicle - 433	Besifloxacin - 433	Besifloxacin - 434	Moxafloxcin - 434
indologenes						
Citrobacter koseri						0/1
Coagulase negative staph	0/1			1/1		
Corynebacterium afermentans						1/1
Corynebacterium amycolatum						1/1
Corynebacterium argentoratense	0/1					1/1
Corynebacterium auris					1/1	
Corynebacterium bovis						
Corynebacterium jeikeium				2/2		
Corynebacterium macginleyi	0/1			1/1	0/1	1/3
Corynebacterium minutissimum				1/1	1/1	
Corynebacterium propinquum	0/1			1/1		3/4
Corynebacterium pseudodiphtheriticum		0/1			4/4	0/3
Corynebacterium species					2/2	0/1
Corynebacterium striatum				3/3	1/2	2/3
Corynebacterium urealyticum			1/1		1/1	
Eikenella corrodens					1/1	
Enterobacter cloacae				1/1		
Enterobacter intermedius						
Enterobacter sakazakii		0/1				
Entercocccus faecalis		0/1			0/2	2/2
Escherichia hermannii						
Gemella morbillorum				1/1	0/1	
Gemella species				2/2		
Granulicatella adiacens					2/2	1/2
Haemophilus haemolyticus						

Organism	Vehicle - 373	Besifloxacin - 373	Vehicle - 433	Besifloxacin - 433	Besifloxacin - 434	Moxafloxcin - 434
Haemophilus influenzae	11/21	21/25	48/66	56/63	73/81	82/88
Haemophilus parainfluenzae	1/2			1/1		2/2
Klebsiella denitrificans					1/1	
Klebsiella oxytoca				1/2		
Klebsiella ozarnae					0/1	
Klebsiella pneumoniae						
Kocuria kristine			1/1		1/1	
Leminorella species						1/1
Micrococcus species			0/1		1/1	
Moraxella catarrhalis	0/1		3/3	1/1	2/2	4/5
Moraxella lacunta			2/3	1/1	4/4	1/1
Moraxella nonliquefaciens						1/1
Moraxella species						1/1
Morganella morganii						1/1
Neisseria gonorrhoeae					2/2	
Neisseria meningitidis	0/1			1/1	1/1	
Neisseria mucosa						
Neisseria sicca					1/1	
Neisseria subflava						1/1
Ochrobactrum anthropi						
Pasteurella multocida			0/1			1/3
Proteus mirabilis					1/1	2/4
Providencia rettgeri						
Pseudomonas aeruginosa			1/1	2/2	1/2	2/3
Pseudomonas fluoresceins						1/1
Rhodococcus species						
Rothia mucilaginosa				1/1		
Serratia marcescens	0/1	0/1		2/2		5/5
Serratia species						
Staphylococcus aureus	2/9	4/6	23/32	17/23	50/58	41/57
Staphylococcus						

Organism	Vehicle - 373	Besifloxacin - 373	Vehicle - 433	Besifloxacin - 433	Besifloxacin - 434	Moxafloxcin - 434
auricularis						
Staphylococcus capitis		0/1			1/3	1/1
Staphylococcus caprae			1/1	1/1	1/1	1/1
Staphylococcus chromogenes						1/1
Staphylococcus epidermidis	0/4	1/2	16/18	13/16	21/29	34/41
Staphylococcus haemolyticus			1/1		1/1	0/1
Staphylococcus hominis			1/2	2/2	3/4	0/1
Staphylococcus intermedius		0/1				
Staphylococcus lugdunensis				1/1	5/5	1/2
Staphylococcus simulans						
Staphylococcus warneri			0/1	1/1	2/2	1/1
Staphylococcus xylosus				1/1		0/1
Stenotrophomonas maltophilia	0/1	0/1		1/1	3/3	3/3
Stomatoccus mucilaginosus						
Streptococcus agalactiae	0/1					
Streptococcus anginosus					1/1	1/1
Streptococcus anginosus group					1/1	
Streptococcus dysgalactiae			1/1	1/1		
Streptococcus intermedius						
Streptococcus millerigroup			1/1			
Streptococcus mitis	0/1		2/4	6/6	3/3	3/5
Streptococcus mitis group		1/1	9/10	7/9	10/11	14/14
Streptococcus oralis	1/1	0/2	0/1	2/3	5/6	4/4
Streptococcu parasanguinis					1/1	1/1
Streptococcus pneumoniae	5/14	15/24	45/66	60/74	51/58	53/64
Streptococcus pyogenes			1/2	0/1		2/2
Streptococcus			2/2	3/3	1/2	2/2

Organism	Vehicle - 373	Besifloxacin - 373	Vehicle - 433	Besifloxacin - 433	Besifloxacin - 434	Moxafloxcin - 434
salivarius						
Streptococcus sanguis				1/2	1/2	
Streptococcus thermophilus					1/1	
Streptococcus species			2/4	1/2	3/3	2/4
Streptococcus viridans			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*

Aerobic and facultative Gram-negative microorganisms: *Haemophilus influenzae; Moraxella lacunata**

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

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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=<0.0001 / <0.0001 [2]
Bacterial Eradication	54 (90%)	28 (48%)	(24.93%, 58.52%)[3]
Visit 3 - Day 8 (+ 1 day)[1]	N=60	N=58	p=0.0003 / 0.0006 [2]
Bacterial Eradication	53 (88%)	35 (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 ± 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=199	N=191	p= <0.0001 / 0.0001 [2]
Bacterial Eradication	176 (88%)	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 ± 1 day)[1]	N=255	N=278	p= <0.0001 / < 0.0001 [2]
Bacterial Eradication	241 (95%)	250 (90%)	(-0.01%, 9.17%)[3]
Visit 3 (Day 8 + 1 day)[1]	N=255	N=278	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 above.

6.1.6 Other Endpoints

No additional endpoints were required to establish the efficacy of the drug product.

6.1.7 Subpopulations - Pediatric Efficacy Data

Clinical Resolution Age less than 2

	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 less than 2

	Besifloxacin	Besi Vehicle	
Visit 2	N= 19	N= 14	p= <0.0267 / < 0.0152[1]
Microbial Eradication	14 (74%)	4 (29%)	(9.34%, 80.88%)[2]
Visit 3 - Day 8 (+ 1 day)	N=19	N=14	p= <0.3853 / 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.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There are no additional dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

6.1.10 Additional Efficacy Issues/Analyses

No additional analyses were required.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate 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.

7.1.2 Adequacy of Data

A Division of Scientific Investigations (DSI) audit was requested. Bausch & Lomb Incorporated terminated the two sites, Zosa and Asbell, early in the trials. If the data from Zosa and Asbell are excluded, there is no significant change in either the safety or efficacy conclusions for this NDA. An audit of the analytical and clinical portions of Studies 373, 433, and 434 noted minor regulatory violations in three of the four sites selected for audit because of the size of enrollment; these sites inspected by DSI (Rigel, Heller, McGriff, and Kanengiser) have violations which do not significantly affect the overall reliability of safety and efficacy data. See the original DSI review dated February 23, 2009.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

A complete listing of adverse events by treatment group with a comparison of incidence is in the Averse Event section. (Section 7.3.3)

7.2 Adequacy of Safety Assessments

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

See Section 7.5.1 The Patient Exposure and Safety Assessments were adequate.

7.2.2 Explorations for Dose Response

The dose of besifloxacin studied in the clinical trial was 0.6%. Refer to Section 7.5.1 for patient exposure.

7.2.3 Special Animal and/or In Vitro Testing

The ocular tolerability of besifloxacin ophthalmic suspension was shown to be favorable in rabbits and dogs after four times daily topical repeat dosing for 28 days.

Minimal effects were observed following oral systemic administration for 28 days of high doses of besifloxacin (up to 500 mg/kg/day). Minor urinary changes (increased urinary proteins and decreased pH) and decreased heart weight at 500 mg/kg were the primary effects in the rat while emesis, increased salivation, and transient facial swelling coupled with pupillary dilation were observed in the dog. No bones or joints alterations were observed. Systemic NOAELs following repeat oral dosing were 500 mg/kg and 5 mg/kg in rats and dogs, respectively. The NOAEL for increased QT interval duration was 10 mg/kg in dogs. Although potential phototoxic effects were observed after oral dosing in mice, no photo-irritant effects were seen when besifloxacin was administered cutaneously to guinea pigs. Compared with the daily human dose, the calculated safety margin for all endpoints is greater than 150.

7.2.4 Routine Clinical Testing

No clinically significant findings in fasting blood chemistry, hematology and urinalysis were reported.

7.2.5 Metabolic, Clearance, and Interaction Workup

No clinically significant findings in fasting blood chemistry, hematology and urinalysis were reported.

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

Besifloxacin is only commercially available for topical ophthalmic administration. While anaphylaxis or other hypersensitivity reactions have not been observed with topical ophthalmic use of besifloxacin in humans, the potential for such reactions should be considered since patients with known hypersensitivity to fluoroquinolones were excluded from clinical trials.

7.3 Major Safety Results

7.1.3 Deaths

There were no deaths in the clinical studies.

7.3.2 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.

7.3.3 Dropouts and/or Discontinuations

	Study 373		Study 433		Study 434	
	Vehicle	Besifloxacin	Vehicle	Besifloxacin	Besifloxacin	Moxifloxacin
Randomized (ITT)	132	137	482	475	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 (Modified-Intent-to Treat)	58	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

Adverse Events associated with dropouts

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

7.3.3 Other Significant Adverse Events

Adverse Event Table

	Besifloxacin (N=1192)	Vehicle (N=616)	Moxifloxacin (N=579)
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

	Besifloxacin (N=1192)	Vehicle (N=616)	Moxifloxacin (N=579)
Anterior chamber inflammation	1 (0.1%)	0	0
Blepharitis allergic	0	1 (0.2%0	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%)
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%)

	Besifloxacin (N=1192)	Vehicle (N=616)	Moxifloxacin (N=579)
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%)
Pharygitis 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
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

	Besifloxacin (N=1192)	Vehicle (N=616)	Moxifloxacin (N=579)
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%.

7.3.4 Submission Specific Primary Safety Concerns

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Refer to Section 7.3. for listing of all adverse events.

7.4.2 Laboratory Findings

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.

7.4.3 Vital Signs

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

7.4.4 Electrocardiograms (ECGs)

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.

7.4.5 Special Safety Studies – Pediatric Ocular Adverse Events

Adverse Events Age less than 2
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.

7.4.6 Immunogenicity

Besifloxacin is not expected to be immunogenic.

7.5 Additional Safety Explorations

7.5.1 Human Carcinogenicity

A waiver for carcinogenicity studies was requested because of the low risk to humans.

7.5.2 Human Reproduction and Pregnancy Data

Pregnancy Category C. In an oral embryofetal development study in rats, the No Observable Adverse Effect Level (NOAEL) for besifloxacin was 100 mg/kg/day for both parental and reproductive toxicity based on maternal mortality, decreased uterine weight, increased resorptions and post-implantation loss, and reduced fetal bodyweight together with a delay in fetal ossification at the highest dose of 1000 mg/kg/day. This NOAEL is approximately 3,333 times the highest recommended total daily human ophthalmic dose (based on a three times daily dosing regimen with 50 µL eye drops in both eyes of a 60 kg patient). In a similar study in rabbits, the fetal and maternal NOAEL was 2 mg/kg/day based on abortions and early deliveries, decreased uterine weight, increased resorptions and post-implantation loss and reduced fetal bodyweight at the highest dose of 20 mg/kg/day. This NOAEL is approximately 67 times the highest recommended total daily human ophthalmic dose. In a prenatal and postnatal development study in rats, the NOAEL for parental toxicity was 10 mg/kg/day (approximately 333 times the highest recommended total daily human ophthalmic dose), based on decreased body weight and food intake at 100 mg/kg/day, and the NOAEL for reproductive performance of parental females and development of their pups was 100 mg/kg/day (approximately 3,333 times the highest recommended total daily human ophthalmic dose), based on litter size reduction, decreased survival, developmental retardation, and delayed sexual maturation of the pups at 1000 mg/kg/day. Exposure-based safety factors for embryofetal and prenatal/postnatal development relative to human exposure are greater than 150-fold.

Since there are no adequate and well-controlled studies in pregnant women, besifloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Besifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when besifloxacin is administered to a nursing mother.

7.5.3 Pediatrics and Effect on Growth

The safety and effectiveness of Besivance in infants below one year of age have not been established. The efficacy of Besivance™ in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials (Refer to Sections 6.1.7 and 7.4.5).

There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

7.5.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no abuse potential expected from topical ophthalmic antibacterial drug products.

7.6 Additional Submissions

No additional submissions are required.

On October 2, 2008 the 120 Day Safety Update was filed. There was no other new safety information that would reasonably affect the statements of contraindications, warnings, precautions and adverse reactions in the label.

8 Postmarketing Experience

No postmarketing risk management plan has been submitted, nor is a risk management plan recommended.

9 Appendices

9.1 Literature Review/References

There is no additional contributory information available from the literature. Besifloxacin is a new chemical entity that has not been previously approved or marketed any where in the world.

9.2 Labeling Recommendations

Attached at the end of this review is a revised label with the reviewer's comments in tracked changes.

9.3 Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration met on December 5, 2008 at the Hilton Washington/Rockville 1750 Rockville Pike, Rockville, Maryland. Michael X. Repka, M.D., chaired the meeting. There were approximately 60 audience members in attendance.

Attendance:
Dermatologic and Ophthalmic Drugs Advisory Committee Members present (voting):
Mary A. Majumder, J.D., Ph.D.
Temporary Voting Members:
Natalie Afshari, M.D., FACS ; Warren B. Bilker, Ph.D.; William G. Gates, M.D.; Philip Lavin, Ph.D.; Marijean M. Miller, M.D.; Michael X. Repka, M.D.; M. Roy Wilson, M.D., M.S.; Paula Cofer (Patient Representative)
Industry Representative (non-voting):
Ellen Strahlman, M.D., M.H.Sc
FDA Participants (non-voting):

Edward M. Cox, M.D., MPH; Wiley Chambers, M.D.; Martin Nevitt, M.D., M.P.H.; Rhea Lloyd, M.D.

Open Public Hearing Speaker:

Brandel France deBravo (National Research Center for Women and Families)

The Advisory unanimously recommended approval of besifloxacin hydrochloride ophthalmic suspension, 0.6%.

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6 Page(s) Withheld

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X Draft Labeling (b4)

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/s/

Martin Nevitt
3/4/2009 09:46:34 AM
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William Boyd
3/4/2009 11:18:52 AM
MEDICAL OFFICER