Division of Anti-Infective and Ophthalmology Products Advisory Committee Meeting Besifloxacin Hydrochloride Ophthalmic Suspension, 0.6%

Martin P. Nevitt, M.D., M.P.H.
US Food and Drug Administration
Medical Officer
December 5, 2008

Applicant Information

Applicant: Bausch & Lomb

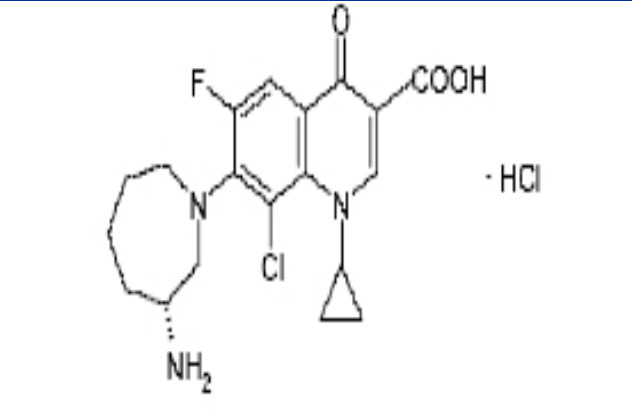
1400 North Goodman Street

Rochester, NY 14609-3547

Introduction and Background

- Besifloxacin is a sterile topical ophthalmic suspension for ocular instillation.

- Besifloxacin: 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; is an 8-chloro fluoroquinolone, a new molecular entity, with anti-infective activity.



Applicant Proposed Indication

- Topical anti-infective indicated for the treatment of bacterial conjunctivitis in subjects ages 1 and older dosed TID for seven days in the affected eye(s)

Drug Information

- Established name: besifloxacin hydrochloride ophthalmic suspension
- NDA Drug Classification: S (Standard review - there are numerous ophthalmic products currently approved for the treatment of bacterial conjunctivitis)
- Pharmacologic Category: Anti-infective, fluoroquinolone
- Dosage Form and Route of Administration: topical ophthalmic suspension

Description of Clinical Trials Which Support Safety and Efficacy of Besifloxacin

- Three adequate and well controlled clinical trials were reviewed to support safety & efficacy (Studies 373, 433 and 434).
- Studies 373 and 433 were multicenter, double-masked, randomized, vehicle-controlled clinical trials (superiority trials), evaluating besifloxacin's clinical and microbial efficacy in the treatment of bacterial conjunctivitis.
- Study 434 was a multicenter, double-masked, randomized active-controlled clinical trial (non-inferiority trial) comparing besifloxacin to moxifloxacin in the treatment of bacterial conjunctivitis
- Each study was conducted under similar but separate protocols.

Description of Clinical Trials Which Support Safety and Efficacy of Besifloxacin

- Studies 373 and 433: besifloxacin, dosed TID for 5 days, was compared with vehicle in subjects who had a clinical diagnosis of bacterial conjunctivitis. (Superiority trials)

- Study 434: besifloxacin dosed TID for 5 days, was compared to moxifloxacin, also dosed TID for 5 days, in subjects who had a clinical diagnosis of bacterial conjunctivitis. (Non-inferiority trial)

Major Inclusion Criteria

(similar for all trials)

- Ages 1 and older.
- Signed IC if ≥ 18; if < 18 signed by representative with assent for subjects ages 6 to 17.
- Clinical diagnosis of acute bacterial conjunctivitis – Minimum score of 1 for ocular discharge and 1 for injection. (Based on a Scale 0 =Absent to 3 = Severe.)
- PH-VA 20/200 or better both eyes (age appropriate testing).
- Willing to discontinue contact lenses, disallowed meds (systemic or topical antimicrobials) for study duration.
- If female with childbearing potential: use reliable contraceptive methods and have had a negative pregnancy test.

Major Exclusion Criteria

(similar for all trials)

- Any uncontrolled systemic or debilitating disease.
- Use of topical ophthalmic solutions, including tear substitutes, within 2 hours before and during the study.
- Use of any ophthalmic topical anti-inflammatory agents within 48 hours before and during study.
- Subjects who were likely to require antimicrobial therapy for another condition, or use of any antibiotic within 72 hours of enrollment.
- Known hypersensitivity to fluoroquinolones or to any of the ingredients in the study meds.
- Subjects with suspected viral or allergic conjunctivitis, or any condition, that could interfere with evaluation of study med.
- History of recurrent corneal erosion syndrome, or active ulcerative keratitis.

Protocol Defined Analysis Populations

- Safety/Intent to Treat (ITT) population- Consisted of all subjects who had a clinical diagnosis of bacterial conjunctivitis randomized to treatment and who had 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) – All mITT population who did not have a major protocol violation. The identification of subjects excluded from the per-protocol population was conducted masked to treatment allocation.

Safety and Efficacy Studies

- In Studies 373, 433 and 434 the total number of subjects included in the Safety/ITT population were:
  - 1,192 in the besifloxacin group
  - 616 subjects in the besifloxacin vehicle
  - 579 subjects in the moxifloxacin group.

Demographics of Patients in Safety/ITT 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)
Gender			
Male	471 (39.5%)	240 (39%)	257 (44.4%)
Female	721 (60.5%)	376 (61%)	322 (55.6%)
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%)

Primary Efficacy Endpoint

- The primary efficacy variable: clinical resolution defined as absence of ocular discharge and bulbar / palpebral conjunctival injection.

- For microbial eradication: efficacy defined as the absence of ocular bacterial species that had been present at or above a certain threshold at baseline.

Primary Efficacy Endpoint

- The Agency recommends the following as a demonstration of efficacy:
  - Statistically significant superiority in replicated studies to the product's vehicle in the cure in the signs and symptoms.
  - Additionally, for the ITT population the cure rate of the vehicle should not be numerically superior to the cure rate of the test product.

Efficacy Endpoint

ITT (i.e., not necessarily culture positive) – Clinical Resolution

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

Efficacy Endpoint

ITT (i.e., not necessarily culture positive) – Clinical Resolution

Study 433	Besifloxacin	Vehicle	
Visit 2 (Day 5 ± 1 day)	N= 475	N= 482	p= 0.0063 / 0.0133[1]
Clinical Resolution	195 (41%)	160 (33%)	(1.73%, 13.99%)[2]
Visit 3 (Day 8 + 1 day)	N= 475	N= 482	p= <0.0001 / <0.0001[1]
Clinical Resolution	374 (79%)	327 (68%)	(5.28%, 16.51%)[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.

Efficacy Endpoint

ITT (i.e., not necessarily culture positive) – Clinical Resolution

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	484 (83%)	480 (83%)	(-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 95% CI for Difference in Percentages; Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Efficacy Endpoint

Modified ITT (i.e., culture positive) – Clinical Resolution

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 =0.2434
2 95% CI difference in proportions
3 Pearson Chi-square Statistic 7.81, exact p-value = 0.0058

Efficacy Endpoint

Modified ITT (i.e., culture positive) – Clinical Resolution

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= 191	N= 173	p= 0.0186 / 0.0038[1]
Clinical Resolution	168 (88%)	132 (76%)	(3.80%, 19.51%)[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.

Efficacy Endpoint

Modified ITT (i.e., culture positive) – Clinical Resolution

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= 243	N= 269	p= 0.0303 / 0.0794[1]
Clinical Resolution	220 (91%)	229 (85%)	(-0.31%, 11.12%)[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 Moxifloxacin. Positive values favor Besifloxacin.

Efficacy Endpoint

Per Protocol (observed cases)

Study 373	Besifloxacin	Vehicle	
Visit 2 (Day 4 ± 1 day)	N= 42	N= 38	p= 0.2869[1]
Clinical Resolution	11 (26%)	6 (16%)	(-0.0724, 0.2804)[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 =0.2869
2 95% CI difference in proportions
3 Pearson Chi-square Statistic 1.80, exact p-value = 0.2629

Efficacy Endpoint

Per Protocol (observed cases)

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.

Efficacy Endpoint

Per Protocol (observed cases)

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

Clinical Microbiology – Bacterial Eradication
(eradication of all pathogens above a pathologic 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%)	27 (47%)	(26.53%, 60.37%)[3]
Visit 3 (Day 8 + 1 day)	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 Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.
3 95% CI - Difference in Percentages; Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Clinical Microbiology – Bacterial Eradication
(eradication of all pathogens above a pathologic threshold at baseline)

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)	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 Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.
3 95% CI - Difference in Percentages; Difference calculated as Besifloxacin minus Vehicle. Positive values favor Besifloxacin.

Clinical Microbiology – Bacterial Eradication (eradication of all pathogens above a pathologic threshold at baseline)

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)	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 Cochran-Mantel-Haenszel test stratified by center / Pearson chi-squared test, resp.
3 95% CI - Difference in Percentages; Difference calculated as Besifloxacin minus Moxifloxacin. Positive values favor Besifloxacin.

Clinical Microbial – Bacterial Eradication for Labeling

Criteria for labeling:

- 1) ≥ 50% eradication rate when ≥ 10 cases identified
- 2) ≥ 80% eradication rate when 5- 9 cases* (organisms labeled with an asterisk*).

- Organisms cultured in < 5 cases are not listed in the label.

Clinical Microbial – Bacterial Eradication for Labeling

- 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**
- *Haemophilus influenzae*
- *Moraxella lacunata.**

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

Integrated Review of Safety

- Studies 373, 433 and 434 were used to establish the Safety and Efficacy of the drug
- All of these trials were randomized, multi-center, double-masked and parallel-group.

Disposition of Patients in Safety/ITT Population

	Study 373		Study 433		Study 434	
	Vehicle	Besi.	Vehicle	Besi.	Besi.	Moxifloxacin
Randomized	132	137	484	473	582	579
Primary Reason for Discontinuation						
Adverse Event	1		5	4	11	5
Protocol Violation		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

Serious AEs in Clinical Trials

- There were only 4 serious adverse events reported:
  - one hospitalization for dehydration
  - another hospitalized for pneumonia
  - and another for CHF;
  - there was one moxifloxacin subject hospitalized for an acute viral illness.
- There were no other serious adverse events reported and no deaths.

Adverse Events

- Few adverse events reported.
- Individual adverse events reported were all less than 2% except:
  - blurred vision reported in 2.1%.
- Other frequently reported adverse events were:
  - eye pain 1.8%, eye irritation 1.4%, and eye pruritis 1.1%.

- Overall, there were no significant differences based on age, gender or race for safety or efficacy.

Post-marketing Experience

- Besifloxacin is not marketed in any country; therefore there are no other sources of AE information.

Questions for the Advisory Committee

- For besifloxacin ophthalmic suspension do you think the benefits outweigh the risks for the treatment of bacterial conjunctivitis?
- If no, what additional studies should be performed?
- Do you have any suggestions concerning the labeling of the product?

Division of Anti-Infective and Ophthalmology Products Advisory Committee Meeting for Besifloxacin

Martin P. Nevitt, M.D., M.P.H.
US Food and Drug Administration
Medical Officer
December 5 , 2008