U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 22308 |
| **Drug Name:** | Besifloxacin Hydrochloride Ophthalmic Suspension 0.6% |
| **Indication(s):** | Treatment of bacterial conjunctivitis |
| **Applicant:** | Bausch & Lomb |
| **Date(s):** | Submitted: 06/02/08 |
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**Keywords:**

NDA, Superiority, Non-inferiority

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

In this submission, the sponsor seeks approval of besifloxacin hydrochloride ophthalmic suspension, 0.6% as base, for the treatment of bacterial conjunctivitis. The Sponsor submitted three pivotal studies: study #373, study #433, and study #434. Both study #373 and study #433 are randomized, double blind, multi-center, and vehicle-controlled superiority trials; study 434 is a randomized, double-blind, multi-center, and active controlled non-inferiority trial with Vigamox (moxifloxacin hydrochloride 0.5% ophthalmic solution) as the active comparator.

In study #373, at Visit 3 (Day 8, +1 day), the clinical resolution rate for besifloxacin hydrochloride ophthalmic suspension, 0.6% as base vs. Vehicle was 61.7% vs. 35.7%, a 26% treatment difference with 95% confidence interval of (8.4%, 43.5%); and for the bacterial eradication rate was 90.0% vs. 69.1%, a 20.9% treatment difference with 95% CI of (6.5%, 35.3%). The study results demonstrated that besifloxacin suspension was statistically superior to vehicle in both clinical resolution and eradication of baseline bacterial infection at Visit 3 (Day 8, +1 day).

In study #433, at Visit 2 (Day 5, ±1 day), the clinical resolution rate for besifloxacin hydrochloride ophthalmic suspension, 0.6% as base vs. Vehicle was 45.2% vs. 33.0%, a 12.2% treatment difference with 95% confidence interval of (2.5%, 22.0%); and the bacterial eradication rate was 91.5% vs. 59.7%, a 31.8% treatment difference with 95% CI of (23.2%, 40.3%). The study results demonstrated that besifloxacin suspension was statistically superior to vehicle in both clinical resolution and eradication of baseline bacterial infection at Visit 2 (Day 5, ±1 day).

There is one major statistical issue for this submission: the choice of non-inferiority margin for the study #434 which uses Vigamox (moxifloxacin hydrochloride 0.5% ophthalmic solution) as the comparator. There is lack of scientific basis for choosing 15% using Vigamox (Moxifloxacin hydrochloride ophthalmic Solution, 0.5%) as the active comparator. Consequently, in study #434, the evidence of efficacy of besifloxacin compared to Vigamox cannot be meaningfully evaluated.

In conclusion, from the results of both study #373 and study #433, this submission provided adequate statistical evidence that besifloxacin hydrochloride ophthalmic suspension (0.6% as base) is superior to vehicle for the treatment of bacterial conjunctivitis. However, we do not recommend reporting the results of the non-inferiority study #434 in the labeling since the evidence of efficacy of Besifloxacin suspension in study #434 cannot be evaluated through the claim of non-inferiority compared to Vigamox using a margin of 15%.

## 1.2 Brief Overview of Clinical Studies

This submission contains three efficacy/safety studies.

Study #373 was a multi-center, double-blinded, randomized, Vehicle-controlled study to evaluate the clinical and microbial efficacy of 0.6% ISV-403 (besifloxacin hydrochloride ophthalmic suspension, 0.6% as base) administered three times daily (TID) for 5 days compared to Vehicle TID for 5 days in the treatment of bacterial conjunctivitis. The primary efficacy endpoints were clinical resolution and bacterial species eradication at Visit 3 (Day 8, +1 Day) in a modified intent-to-treat (mITT) subset based on all randomized subjects who received at least one drop of the study medication and had baseline cultures indicating pathogenic bacterial levels. Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. Bacterial species eradication of baseline bacterial infection was defined as the absence of pre-defined ocular bacterial species by Visit 3. Study #373 was originally proposed by the Sponsor as a Phase II study.

Study #433 was also a multi-center, double-blinded, randomized, Vehicle-controlled study to evaluate the clinical and microbial efficacy of 0.6% ISV-403 (besifloxacin hydrochloride ophthalmic suspension, 0.6% as base) administered three times daily (TID) for 5 days compared to Vehicle TID for 5 days in the treatment of bacterial conjunctivitis. The primary efficacy endpoints were clinical resolution and bacterial species eradication at Visit 2 (Day 5, ±1 Day) in a modified intent-to-treat subset based on all randomized subjects who received at least one drop of the study medication and had baseline cultures indicating pathogenic bacterial levels. Clinical resolution was defined as the absence of conjunctival discharge and bulbar conjunctival injection. Bacterial eradication was indicated by the absence of pre-defined ocular bacterial species that were present at or above threshold at baseline.

Study #434 was a multi-center, double-blinded, randomized, active-controlled, parallel-group study to compare the safety and efficacy of besifloxacin ophthalmic suspension administered TID to the fluoroquinolone Vigamox TID for the treatment of bacterial conjunctivitis. The primary efficacy endpoints were clinical resolution and bacterial species eradication at Visit 2 (Day 5, ±1 Day) in a modified intent-to-treat subset based on all randomized subjects who received at least one drop of the study medication and had baseline cultures indicating pathogenic bacterial levels. Clinical resolution was defined as the absence of conjunctival discharge and bulbar conjunctival injection. Bacterial eradication was indicated by the absence of pre-defined ocular bacterial species that were present at or above threshold at baseline. For both primary efficacy endpoints, the non-inferiority margin was chosen as 15%.

## 1.3 Statistical Issues and Findings

There is one major statistical issue for this submission: the choice of non-inferiority margin for the non-inferiority study #434.

**Choice of Non-inferiority Margin of 15% in Study #434**

Regarding when a non-inferiority trial design would be appropriate and how the non-inferiority margin should be based on, ICH E10 guideline states the following:

"The non-inferiority trial design is appropriate and reliable only when the historical estimate of drug effect size can be well supported by reference to the results of previous studies of the control drug."

"The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial. If a difference between active control and the new drug favors the control by as much as or more than this margin, the new drug might have no effect at all. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence."

"The determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment, should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative."

"There are many conditions, however, in which drugs considered effective cannot regularly be shown superior to placebo in well-controlled trials; and one therefore cannot reliably determine a minimum effect the drug will have in the setting of a specific trial. Such conditions tend to include those in which there is substantial improvement and variability in placebo groups, and/or in which the effects of therapy are small or variable...."

For study #434, a non-inferiority margin of 15% was used. The margin was recommended to the sponsor by the FDA clinical review team.

However, there is not a sufficient scientific justification for the 15% margin. The active comparator Vigamox (Moxifloxacin hydrochloride ophthalmic Solution, 0.5%) was approved in 2003. The original approval for Vigamox was based on one superiority study compared with a vehicle control, and one non-inferiority study compared with ocuflox ophthalmic solution. In the superiority trial, the clinical cure rate for patients who had baseline bacterial infection confirmed at end of therapy (Day 5) was 66% (95/143) for Vigamox, and 51% (74/144) for vehicle. The treatment difference was 15% with 95% confidence interval of (3.8%, 26.3%). With the effect size could be only 4% for the active control, a choice of 15% does not have any statistical reasoning. Therefore, there is lack of scientific basis for choosing 15% using Vigamox as the active comparator. Consequently, in study 434, the evidence of efficacy of besifloxacin compared to Vigamox cannot be meaningfully evaluated.

## 2. INTRODUCTION

### 2.1 Overview

Besifloxacin hydrochloride is a fluoroquinolone which has been shown to be active against a wide range of aerobic bacteria. Structurally, Besifloxacin has an N-1 cyclopropyl group, which provides broad-spectrum activity against aerobic bacteria. The activity is enhanced by a chloride substituent at C-8. Recent data indicate that the C-8 chloride improves activity against both DNA gyrase and topoisomerase IV enzymes. The inhibition of these two enzymes is the main mechanism behind the bactericidal effects of this fluoroquinolone. Unlike other currently available topical antibiotics/anti-infectives for the treatment of bacterial conjunctivitis, such as ofloxacin and ciprofloxacin, which are dosed as frequently as 8 times per day initially and then tapered to 4 times per day for the remainder of the treatment period, besifloxacin ophthalmic suspension was developed to be dosed 3 times daily (TID). This treatment regimen may provide efficacy, enhance subject convenience, and improve compliance.

This submission contains three efficacy/safety studies. Study #373 is a multi-center, double-blinded, randomized, Vehicle-controlled study to evaluate the clinical and microbial efficacy of 0.6% ISV-403 (besifloxacin hydrochloride ophthalmic suspension, 0.6% as base) administered three times daily (TID) for 5 days compared to Vehicle TID for 5 days in the treatment of bacterial conjunctivitis. This study was originally designed as a Phase II study. Study #433 is also a multi-center, double-blinded, randomized, Vehicle-controlled study to evaluate the clinical and microbial efficacy of 0.6% ISV-403 (besifloxacin hydrochloride ophthalmic suspension, 0.6% as base) administered three times daily (TID) for 5 days compared to Vehicle TID for 5 days in the treatment of bacterial conjunctivitis. Study #434 is a multi-center, double-blinded, randomized, active-controlled, parallel-group study to compare the safety and efficacy of besifloxacin ophthalmic suspension administered TID to another fluoroquinolone Vigamox TID for the treatment of bacterial conjunctivitis.

### 2.2 Data Sources

The Sponsor's study reports for studies #373, #433, and #434 are available on the EDR at \\Cdsesub1\EVSPROD\NDA022308.

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design and Endpoints

<u>Study #373</u>

Study #373 was a multi-center, randomized, double-masked, parallel-group, Vehicle-controlled clinical trial to evaluate the clinical and microbial efficacy of 0.6% besifloxacin hydrochloride ophthalmic suspension administered TID for 5 days compared to Vehicle TID for 5 days in the treatment of bacterial conjunctivitis. This study was designed as a Phase II clinical trial. The

primary objective of this study was to determine if 0.6% ISV-043 used three times a day for five days effectively treats bacterial conjunctivitis.

Subjects who met the criteria for enrollment were randomly assigned to use either besifloxacin hydrochloride ophthalmic suspension, 0.6% as base, or its Vehicle TID for five days in a 1:1 ratio. The study consisted of three visits: Visit 1 (Eligibility/Baseline) took place on the first treatment day (Day 1), Visit 2 on the fourth treatment day (Day 4 (± 1 day)) and Visit 3 (Day 8 (+ 1 day)) at least 48 hours after completing 5 days of study drug use.

A patient was considered as having bacterial conjunctivitis if the subject had a clinical diagnosis of acute 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.

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. Bacterial species eradication of baseline bacterial infection was defined as the absence of pre-defined ocular bacterial species by Visit 3. Clinical assessments of ocular signs and symptoms were to be conducted at all three visits. Ocular bacteriological cultures were to be taken at all the three study visits.

The primary objective of this study was to determine if 0.6% ISV-043 used three times a day for five days effectively treats bacterial conjunctivitis. The primary hypothesis was the following:
$H_0$: Subjects treated with ISV-403 and those treated with Vehicle will have the same proportion of subjects with bacterial eradication and the same proportion of subjects with clinical resolution.
$H_1$: Subjects treated with ISV-403 and Vehicle will not have the same proportions of subjects with bacterial eradication and clinical resolution.)

**Study #433**

Study #433 was a multi-center, randomized, double-masked, parallel-group, Vehicle-controlled clinical trial to evaluate the clinical and microbial efficacy of besifloxacin hydrochloride ophthalmic suspension, 0.6% as base, compared to vehicle when instilled TID, for 5 days, in the treatment of bacterial conjunctivitis.

Eligible subjects were randomized (1:1) to receive besifloxacin ophthalmic suspension or vehicle and instructed to instill 1 drop of study drug, at approximately 6 hour intervals, TID, for 5 days. Subjects participated in 3 study visits at Day 1, Day 5 (±1 day), and Day 8 (+1 day). All visits, except Visit 1 (Day 1) were scheduled to occur between 7 AM and 10 AM. Assessments included visual acuity (VA), biomicroscopy (including a clinical assessment of ocular discharge and conjunctival injection), direct ophthalmoscopy, and microbial cultures.

A patient was considered as having bacterial conjunctivitis if the subject had a clinical diagnosis of acute 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 bulbar conjunctival injection.

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.

Ocular discharge was defined and scored as the following:

0 = Absent

1 = Mild: Small amount of mucopurulent or purulent discharge noted in the lower cul-de-sac. No true matting of the eyelids in the morning upon awakening.

2 = Moderate: Moderate amount of mucopurulent or purulent discharge noted in the lower cul-de-sac. Frank matting together of the eyelids in the morning upon awakening.

3 = Severe: Profuse amount of mucopurulent or purulent discharge noted in the lower cul-de-sac and in the marginal tear strip. Eyelids tightly matted together in the morning upon awakening, requiring warm soaks to pry the lids apart.

Bulbar conjunctival injection was assessed by evaluating 4 quadrants (inferior, superior, temporal, and nasal). Standardized photographs for grading conjunctival injection were provided to Investigators who used the following scale:

0 = Normal: Normal vascular pattern

1 = Mild: Awareness eye is slightly pink in any 1 quadrant

2 = Moderate: Diffuse pink color in at least 3 quadrants

3 = Severe: Vasodilation in at least 3 quadrants, reddish hue

Clinical outcome was defined and scored as the following

0 = Resolution: Sum of scores for ocular discharge and bulbar conjunctival injection equal zero

1 = Improvement: Sum of scores for ocular discharge and bulbar conjunctival injection less than the corresponding sum at baseline

2 = No Change: Sum of scores for ocular discharge and bulbar conjunctival injection equal to the corresponding sum at baseline

3 = Worse: Sum of scores for ocular discharge and bulbar conjunctival injection greater than the corresponding sum at baseline

Microbial outcome was measured on an ordinal 0a to 3b eradication scale:

- 0a: Eradication (infecting organism originally present at or above threshold on Day 1 and absent in follow-up culture) without a 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 a 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 remaining present at or above threshold, but not exceeding the Day 1 count in follow-up culture) without a new isolate at or above threshold
- 2b: Persistence (infecting organism originally present at or above threshold on Day 1, and remaining present at or above threshold, but not exceeding the Day 1 count in follow-up culture) with a 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

Study #433 is similar to study #373 with the following exceptions: in study #373, the definition of clinical manifestation of bacterial conjunctivitis required a grade of at least 1 for ocular discharge and a grade of at least 1 for either bulbar conjunctival injection or palpebral conjunctival injection; the definition of clinical resolution is based on the sum score of the 3 clinical signs identified above; the day of Visit 2 is Day 4 (± 1 day); and the visit used for primary efficacy is the last observation carried forward for Visit 3, Day 8 (+1 day).

**Study #434**

Study #434 was a multi-center, double-blinded, randomized, active-controlled, parallel-group study to compare the safety and efficacy of besifloxacin ophthalmic suspension administered TID to the fluoroquinolone Vigamox TID for the treatment of bacterial conjunctivitis. Besifloxacin hydrochloride ophthalmic suspension, 0.6% as base was considered non-inferior to Vigamox if the 95% (two-sided) CI for the difference in response rates between two treatment groups contained zero and the lower limit of the CI was greater than -15%. According to the Sponsor, Vigamox (manufactured by Alcon Laboratories Incorporated, Fort Worth, Texas, US) was selected as the active control for this study because it is a leading ophthalmic solution indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of aerobic gram-positive microorganisms, aerobic gram-negative microorganisms, and other microorganisms.

Eligible subjects were randomized (1:1) to receive besifloxacin ophthalmic suspension or Vigamox and instructed to instill 1 drop of study drug, at approximately 6 hour intervals, TID, for 5 days. Subjects participated in 3 study visits at Day 1, Day 5 (±1 day), and Day 8 (+1 day). All visits, except Visit 1 (Day 1) were scheduled to occur between 7 AM and 10 AM. Assessments included visual acuity (VA), biomicroscopy (including a clinical assessment of ocular discharge and conjunctival injection), direct ophthalmoscopy, and microbial cultures.

A patient was considered as having bacterial conjunctivitis if the subject had a clinical diagnosis of acute 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 bulbar conjunctival injection.

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.

The definition and scoring scale of ocular discharge, bulbar conjunctival injection, clinical outcome, and microbial outcome were the same as study #434.

### 3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Study #373

A total of 270 subjects entered the study at 35 centers located in the United States. Of these, 269 subjects were randomized (137 to receive 0.6% ISV-403 (besifloxacin hydrochloride ophthalmic suspension) [50.9%] and 132 [49.1%] to receive Vehicle). One (1) subject who would not allow the investigator to collect a culture of the conjunctiva was not randomized. One hundred eighteen subjects with bacteriologically confirmed acute bacterial conjunctivitis at baseline (Visit 1) were eligible for the mITT population. Of these, two subjects withdrew from the study before Visit 2. Sixty (50.8%) of these subjects were randomized to 0.6% ISV-403 and 58 (49.2%) were randomized to Vehicle. Two subjects did not have a bacteriological culture at Visit 2, and one did not have a bacteriological culture at Visit 3.

**Table 1: Study 373 Disposition of all enrolled subjects**

| | Besifloxacin Suspension | Vehicle | Total |
|---|---|---|---|
| | (N=137) | (N=132) | (N=269) |
| Total Number of Subjects | | | |
| Randomized | 137 (100.0%) | 132 (100.0%) | 269 (100.0%) |
| Completed | 134 (97.8%) | 122 (92.4%) | 256 (95.2%) |
| Discontinued | 3 (2.2%) | 10 (7.6%) | 13 (4.8%) |
| Primary Reason for Discontinuation | | | |
| AE/intercurrent illness | 0 (0.0%) | 1 (0.8%) | 1 (0.4%) |
| Protocol deviation/violation | 1 (0.7%) | 0 (0.0%) | 1 (0.4%) |
| Insufficient therapeutic response | 1 (0.7%) | 7 (5.3%) | 8 (3.0%) |
| Lost to Follow-up | 1 (0.7%) | 0 (0.0%) | 1 (0.4%) |
| Refusal | 0 (0.0%) | 1 (0.8%) | 1 (0.4%) |
| Termination by site or study sponsor | 0 (0.0%) | 1 (0.8%) | 1 (0.4%) |

Source: Sponsor's study #373 report Table 8.1.1-1

Summary of analysis population was presented in the following table. 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. 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.

**Table 2: Study #373 Analysis Population by Treatment Arm**

| | All randomized | mITT | |
|---|---|---|---|
| | N | n | (% of N) |
| Besifloxacin Suspension | 137 | 60 | 43.8% |
| Vehicle | 132 | 58 | 43.9% |
| Total | 269 | 118 | 43.9% |

**Table 3: Study #373 Demographics**

**Safety Population**

| | | Besifloxacin Suspension (N=137) | | Vehicle (N=132) | | Total (N=269) | |
|---|---|---|---|---|---|---|---|
| | | N | (%) | n | (%) | n | (%) |
| **Gender** | **Male** | 51 | (37.2) | 56 | (42.4) | 107 | (39.8) |
| | **Female** | 86 | (62.8) | 76 | (57.6) | 162 | (60.2) |
| **Age** | **Mean** | | 33.3 | | 35.1 | | 34.2 |
| | **SD** | | 22.3 | | 22.4 | | 22.3 |
| | **Median** | | 30.0 | | 31.0 | | 31.0 |
| | **Range** | | 1 to 92 | | 1 to 81 | | 1 to 92 |
| **Race** | **Caucasian** | 116 | (84.7) | 106 | (80.3) | 222 | (82.5) |
| | **Black or African American** | 6 | (4.4) | 11 | (8.3) | 17 | (6.3) |
| | **Asian** | 2 | (1.5) | 2 | (1.5) | 4 | (1.5) |
| | **Hispanic** | 12 | (8.8) | 8 | (6.1) | 20 | (7.4) |
| | **Other** | 1 | (0.7) | 5 | (3.8) | 6 | (2.2) |

**mITT Population**

| | | Besifloxacin Suspension (N=60) | | Vehicle (N=58) | | Total (N=118) | |
|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) |
| **Gender** | **Male** | 25 | (41.7) | 27 | (46.6) | 52 | (44.1) |
| | **Female** | 35 | (58.3) | 31 | (53.4) | 66 | (55.9) |
| **Age** | **Mean** | | 28.7 | | 34.7 | | 31.7 |
| | **SD** | | 23.3 | | 24.0 | | 23.7 |
| | **Median** | | 20.0 | | 30.5 | | 27.5 |
| | **Range** | | 1 to 89 | | 1 to 81 | | 1 to 89 |
| **Race** | **Caucasian** | 48 | (80.0) | 47 | (81.0) | 95 | (80.5) |
| | **Black or African American** | 1 | (1.7) | 6 | (10.3) | 7 | (5.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Asian** | 2 | (3.3) | 0 | (0.0) | 2 | (1.7) |
| **Hispanic** | 8 | (13.3) | 2 | (3.4) | 10 | (8.5) |
| **Other** | 1 | (1.7) | 3 | (5.2) | 4 | (3.5) |

Source: Sponsor's study #373 report Table 9.2-1 and 9.2-2

**Study #433**

A total of 957 subjects were randomized and received at least 1 dose of study drug. These subjects comprised the Safety population (473 besifloxacin ophthalmic suspension and 484 Vehicle). Of those subjects, 874 (91.3%) completed the study; 442 (93.4%) subjects treated with besifloxacin ophthalmic suspension and 432 (89.3%) subjects treated with vehicle. A total of 83 (8.7%) subjects in the Safety population discontinued from the study; 31 (6.6%) subjects treated with besifloxacin ophthalmic suspension and 52 (10.7%) subjects treated with Vehicle.

A total of 26 subjects were not treated with the study drug to which they were randomized. Fourteen (14) subjects randomized to the besifloxacin ophthalmic suspension treatment group received vehicle and 12 subjects randomized to vehicle received besifloxacin ophthalmic suspension. These subjects were differentiated in the primary analysis set by referring as either 'as treated' or 'as randomized'.

**Table 4: Study #433 Disposition of all randomized subjects**

| | Besifloxacin Suspension | Vehicle | Overall |
|---|---|---|---|
| Total Number of Subjects | N=475 | N=482 | N=957 |
| Randomized | 475 (100.0%) | 482 (100.0%) | 957 (100.0%) |
| Treated | 473[1] (99.6%) | 484[1] (100.4%) | 957 (100.0%) |
| As Randomized | 461 (97.5%) | 470 (97.1%) | 931 (97.3%) |
| Not As Randomized | 12 (2.5%) | 14 (2.9%) | 26 (2.7%) |
| Included in All Randomized Population | 473[1] (99.6%) | 484[1] (100.4%) | 957 (100.0%) |
| Completed | 442 (93.4%) | 432 (89.3%) | 874 (91.3%) |
| Discontinued | 31 (6.6%) | 52 (10.7%) | 83 (8.7%) |
| Primary Reason for Discontinuation | | | |
| Adverse Event | 4 (0.8%) | 5 (1.0%) | 9 (0.9%) |
| Lack of efficacy | 3 (0.6%) | 14 (2.9%) | 17 (1.8%) |
| Lost to follow-up | 10 (2.1%) | 16 (3.3%) | 26 (2.7%) |
| Subject withdrew consent | 10 (2.1%) | 16 (3.3%) | 26 (2.7%) |
| Other | 4 (0.8%) | 8 (1.7%) | 12 (1.3%) |

[1] Fourteen (14) subjects randomized to the besifloxacin ophthalmic suspension treatment group received vehicle and 12 subjects randomized to vehicle received besifloxacin ophthalmic suspension.
Source: Sponsor's study #433 report Table 4

Summary of analysis population was presented in the following table. The Intent to Treat (ITT) study population (n=957) included all randomized subjects. The modified ITT (mITT) study population (n=390) included all subjects in the ITT study population for whom baseline cultures in at least 1 eye indicated bacteria levels at or above threshold for any accepted ocular species. The Per Protocol (PP) study population will include those subjects in the mITT study population who completed the study, and for whom no major protocol violations are noted.

**Table 5: Study #433 Analysis Population by Treatment Arm**

| | ITT (All randomized) | mITT | | PP | |
|---|---|---|---|---|---|
| | N | n | % of N | n | % of N |
| Besifloxacin Suspension | 475 | 199 | (41.9) | 151 | (31.9) |
| Vehicle | 482 | 191 | (39.6) | 133 | (27.6) |
| Total | 957 | 390 | (40.8) | 284 | (29.7) |

**Table 6: Study #433 Demographics**

| ITT Population | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Besifloxacin Suspension (N=475) | | Vehicle (N=482) | | Total (N=957) | |
| | | n | (%) | n | (%) | n | (%) |
| **Gender** | **Male** | 173 | (36.4) | 182 | (37.8) | 355 | (37.1) |
| | **Female** | 302 | (63.6) | 300 | (62.2) | 602 | (62.9) |
| **Age** | **Less than 2 years** | 21 | (4.4) | 20 | (4.1) | 41 | (4.3) |
| | **2 to 9 years** | 109 | (22.9) | 114 | (23.7) | 223 | (23.3) |
| | **10 to 19 years** | 87 | (18.3) | 82 | (17.0) | 169 | (17.7) |
| | **20 to 29 years** | 64 | (13.5) | 66 | (13.7) | 130 | (13.6) |
| | **30 to 39 years** | 60 | (12.6) | 71 | (14.7) | 131 | (13.7) |
| | **40 to 49 years** | 50 | (10.5) | 50 | (10.4) | 100 | (10.4) |
| | **50 to 59 years** | 38 | (8.0) | 39 | (8.1) | 77 | (8.0) |
| | **60 years or Older** | 46 | (9.7) | 40 | (8.3) | 86 | (9.0) |
| | **MEAN** | | 27.3 | | 27.3 | | |
| | **SD** | | 21.8 | | 21.7 | | |
| | **RANGE** | | 1 to 98 | | 0 to 97 | | |
| **Ethnicity** | **Not Hispanic or Latino** | 348 | (73.3) | 356 | (73.9) | 704 | (73.6) |
| | **Hispanic or Latino** | 127 | (26.7) | 126 | (26.1) | 253 | (26.4) |
| **Race** | **American Indian or Alaskan Native** | 1 | (0.2) | 1 | (0.2) | 2 | (0.2) |
| | **Asian** | 10 | (2.1) | 7 | (1.5) | 17 | (1.8) |
| | **Black or African American** | 44 | (9.3) | 46 | (9.5) | 90 | (9.4) |
| | **Native Hawaiian or Pacific Islander** | 1 | (0.2) | 3 | (0.6) | 4 | (0.4) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **White** | 312 | (65.7) | 312 | (64.7) | 624 | (65.2) |
| | **Other** | 107 | (22.5) | 113 | (23.4) | 220 | (23.0) |

**mITT Population**

| | | **Besifloxacin Suspension (N=199)** | | **Vehicle (N=191)** | | **Total (N=390)** | |
|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) |
| **Gender** | **Male** | 75 | (37.7) | 78 | (40.8) | 153 | (39.2) |
| | **Female** | 124 | (62.3) | 113 | (59.2) | 237 | (60.8) |
| **Age** | **Less than 2 years** | 17 | (8.5) | 13 | (6.8) | 30 | (7.7) |
| | **2 to 9 years** | 72 | (36.2) | 71 | (37.2) | 143 | (36.7) |
| | **10 to 19 years** | 25 | (12.6) | 25 | (13.1) | 50 | (12.8) |
| | **20 to 29 years** | 20 | (10.1) | 15 | (7.9) | 35 | (9.0) |
| | **30 to 39 years** | 18 | (9.0) | 17 | (8.9) | 35 | (9.0) |
| | **40 to 49 years** | 20 | (10.1) | 14 | (7.3) | 34 | (8.7) |
| | **50 to 59 years** | 12 | (6.0) | 17 | (8.9) | 29 | (7.4) |
| | **60 years or Older** | 13 | (7.5) | 19 | (9.9) | 32 | (8.2) |
| | **MEAN** | | 22.2 | | 24.4 | | |
| | **SD** | | 22.4 | | 24.0 | | |
| | **RANGE** | | 1 to 98 | | 1 to 87 | | 1 to 98 |
| **Ethnicity** | **Not Hispanic or Latino** | 138 | (69.3) | 150 | (78.5) | 288 | (73.8) |
| | **Hispanic or Latino** | 61 | (30.7) | 41 | (21.5) | 102 | (26.1) |
| **Race** | **American Indian or Alaskan Native** | 1 | (0.5) | 0 | (0.0) | 1 | (0.3) |
| | **Asian** | 3 | (1.5) | 5 | (2.6) | 8 | (2.1) |
| | **Black or African American** | 18 | (9.0) | 18 | (9.4) | 36 | (9.2) |
| | **Native Hawaiian or Pacific Islander** | 0 | (0.0) | 1 | (0.5) | 1 | (0.3) |
| | **White** | 125 | (62.8) | 126 | (66.0) | 251 | (64.4) |
| | **Other** | 52 | (26.1) | 41 | (21.5) | 93 | (23.8) |

Source: Sponsor's study #433 report Table 7

**Study #434**

A total of 1161 subjects were randomized and received at least 1 dose of study drug. These subjects comprised the Safety population (582 besifloxacin ophthalmic suspension and 579 Vigamox). Of those subjects, 1109 (95.5%) completed the study; 555 (95.4%) subjects randomized to Besifloxacin ophthalmic suspension and 554 (95.7%) subjects to Vigamox. A total of 52 (4.5%) subjects in the Safety population discontinued from the study; 27 (4.6%) and 25 (4.3%) subjects in the besifloxacin ophthalmic suspension and Vigamox treatment groups respectively.

A total of 533 subjects who were randomized, had baseline cultures in at least 1 eye with bacteria levels at or above threshold for any accepted ocular species. These subjects comprised the modified intent to treat (mITT) population (255 besifloxacin ophthalmic suspension and 278

Vigamox). Of those subjects, 511 (95.9%) completed the study; 243 (95.3%) subjects randomized to besifloxacin ophthalmic suspension and 268 (96.4%) subjects to Vigamox. A total of 22 (4.1%) subjects in the mITT population discontinued from the study; 12 (4.7%) and 10 (3.6%) subjects in the besifloxacin ophthalmic suspension and Vigamox treatment groups respectively.

A total of 32 subjects were not treated with the study drug to which they were randomized. Sixteen (16) subjects randomized to the besifloxacin ophthalmic suspension treatment group received Vigamox and 16 subjects randomized to Vigamox received besifloxacin ophthalmic suspension. These subjects were differentiated in the primary analysis set by referring as either 'as treated' or 'as randomized'.

**Table 7: Study #434 Disposition of all randomized subjects**

| | Besifloxacin Suspension | Vehicle | Overall |
|---|---|---|---|
| Total Number of Subjects | N=582 | N=579 | N=1161 |
| Randomized | 582 (100.0%) | 579 (100.0%) | 1161 (100.0%) |
| Treated | 582 (100.0%) | 579 (100.0%) | 1161 (100.0%) |
| As Randomized | 566 (97.3%) | 563 (97.2%) | 1129 (97.2%) |
| Not As Randomized | 16 (2.7%) | 16 (2.8%) | 32 (2.8%) |
| Included in All Randomized Population | 582 (100.0%) | 579 (100.0%) | 1161 (100.0%) |
| Completed | 555 (95.4%) | 554 (95.7%) | 1109 (95.5%) |
| Discontinued | 27 (4.6%) | 25 (4.3%) | 52 (4.5%) |
| Primary Reason for Discontinuation | | | |
| Adverse Event | 11 (1.9%) | 5 (0.9%) | 16 (1.4%) |
| Lack of efficacy | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) |
| Lost to follow-up | 10 (1.7%) | 8 (1.4%) | 18 (1.6%) |
| Subject withdrew consent | 1 (0.2%) | 4 (0.7%) | 5 (0.4%) |
| Other | 4 (0.7%) | 7 (1.2%) | 11 (0.9%) |

Source: Sponsor's study #434 report Table 4

Summary of analysis population was presented in the following table. The Intent to Treat (ITT) study population (n=1161) included all randomized subjects. The modified ITT (mITT) study population (n=533) included all subjects in the ITT study population for whom baseline cultures in at least 1 eye indicated bacteria levels at or above threshold for any accepted ocular species. The Per Protocol (PP) study population will include those subjects in the mITT study population who completed the study, and for whom no major protocol violations are noted.

**Table 8: Study #434 Analysis Population by Treatment Arm**

| | ITT (All randomized) | mITT | | PP | |
|---|---|---|---|---|---|
| | N | n | % of N | n | % of N |
| Besifloxacin Suspension | 582 | 255 | (43.8) | 161 | (27.7) |
| Vehicle | 579 | 278 | (48.0) | 180 | (31.1) |
| Total | 1161 | 533 | (45.9) | 341 | (29.4) |

**Table 9: Study #434 Demographics**

| | | ITT Population | | | | | |
|---|---|---|---|---|---|---|---|
| | | Besifloxacin Suspension (N=582) | | Vigamox (N=579) | | Total (N=1161) | |
| | | n | (%) | n | (%) | n | (%) |
| **Gender** | **Male** | 250 | (43.0) | 256 | (44.2) | 506 | (43.6) |
| | **Female** | 332 | (57.0) | 323 | (55.8) | 655 | (56.4) |
| **Age** | **Less than 2 years** | 22 | (3.8) | 15 | (2.6) | 37 | (3.2) |
| | **2 to 9 years** | 91 | (15.6) | 90 | (15.5) | 181 | (15.6) |
| | **10 to 19 years** | 75 | (12.9) | 81 | (14.0) | 156 | (13.4) |
| | **20 to 29 years** | 93 | (16.0) | 73 | (12.6) | 166 | (14.3) |
| | **30 to 39 years** | 71 | (12.2) | 76 | (13.1) | 147 | (12.7) |
| | **40 to 49 years** | 68 | (11.7) | 59 | (10.2) | 127 | (10.9) |
| | **50 to 59 years** | 63 | (10.8) | 65 | (11.2) | 128 | (11.0) |
| | **60 years or Older** | 99 | (17.0) | 120 | (20.7) | 219 | (18.9) |
| | **Mean** | | 34.1 | | 36.1 | | |
| | **SD** | | 23.5 | | 24.7 | | |
| | **Range** | | 1 to 92 | | 0 to 100 | | |
| **Ethnicity** | **Not Hispanic or Latino** | 510 | (87.6) | 506 | (87.4) | 1016 | (87.5) |
| | **Hispanic or Latino** | 72 | (12.4) | 73 | (12.6) | 145 | (12.5) |
| **Race** | **American Indian or Alaskan Native** | 3 | (0.5) | 6 | (1.0) | 9 | (0.8) |
| | **Asian** | 87 | (14.9) | 89 | (15.4) | 176 | (15.2) |
| | **Black or African American** | 73 | (12.5) | 63 | (10.9) | 136 | (11.7) |
| | **Native Hawaiian or Pacific Islander** | 5 | (0.9) | 2 | (0.3) | 7 | (0.6) |
| | **White** | 385 | (66.2) | 391 | (67.5) | 776 | (66.8) |
| | **Other** | 29 | (5.0) | 28 | (4.8) | 57 | (4.9) |

| mITT Population | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Besifloxacin Suspension (N=255) | | Vigamox (N=278) | | Total (N=533) | |
| | | n | (%) | n | (%) | n | (%) |
| **Gender** | **Male** | 111 | (43.5) | 137 | (49.3) | 248 | (46.5) |
| | **Female** | 144 | (56.5) | 141 | (50.7) | 285 | (53.5) |
| **Age** | **Less than 2 years** | 18 | (7.1) | 12 | (4.3) | 30 | (5.6) |
| | **2 to 9 years** | 62 | (24.3) | 58 | (20.9) | 120 | (22.5) |
| | **10 to 19 years** | 28 | (11.0) | 20 | (7.2) | 48 | (9.0) |
| | **20 to 29 years** | 30 | (11.8) | 22 | (7.9) | 52 | (9.8) |
| | **30 to 39 years** | 24 | (9.4) | 31 | (11.2) | 55 | (10.3) |
| | **40 to 49 years** | 23 | (9.0) | 26 | (9.4) | 49 | (9.2) |
| | **50 to 59 years** | 25 | (9.8) | 29 | (10.4) | 54 | (10.1) |
| | **60 years or Older** | 45 | (17.6) | 80 | (28.8) | 125 | (23.5) |
| | **Mean** | | 31.2 | | 38.7 | | |
| | **SD** | | 25.7 | | 28.0 | | |
| | **Range** | | 1 to 92 | | 0 to 100 | | |
| **Ethnicity** | **Not Hispanic or Latino** | 228 | (89.4) | 242 | (87.1) | 470 | (88.2) |
| | **Hispanic or Latino** | 27 | (10.6) | 36 | (12.9) | 63 | (11.8) |
| **Race** | **American Indian or Alaskan Native** | 2 | (0.8) | 3 | (1.1) | 5 | (0.9) |
| | **Asian** | 34 | (13.3) | 44 | (15.8) | 78 | (14.6) |
| | **Black or African American** | 29 | (11.4) | 25 | (9.0) | 54 | (10.1) |
| | **Native Hawaiian or Pacific Islander** | 2 | (0.8) | 1 | (0.4) | 3 | (0.6) |
| | **White** | 178 | (69.8) | 195 | (70.1) | 373 | (70.0) |
| | **Other** | 10 | (3.9) | 10 | (3.6) | 20 | (3.8) |

Source: Sponsor's study #434 report Table 6

### 3.1.3 Statistical Methodologies

#### 3.1.3.1 Study #373

**Analysis of Primary Efficacy Endpoints**

The primary efficacy endpoints were clinical resolution and eradication of baseline bacterial infection at Visit 3 (Day 8 visit). Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. Bacterial species eradication of baseline bacterial infection was defined as the absence of pre-defined ocular bacterial species by Visit 3. Clinical assessments of ocular signs and symptoms were to be conducted at all three visits. Ocular bacteriological cultures were to be taken at all the three study visits.

The primary hypothesis was the following:

$H_0$: Subjects treated with ISV-403 and those treated with Vehicle will have the same proportion of subjects with bacterial eradication and the same proportion of subjects with clinical resolution.
$H_1$: Subjects treated with ISV-403 and Vehicle will not have the same proportions of subjects with bacterial eradication and clinical resolution.)

The primary analytic method used in the analysis of these endpoints was a Cochran-Mantel-Haenszel (CMH) statistic stratifying by center.

**Efficacy Analysis Sets**

All analyses were to be performed on a modified intent-to-treat (mITT) basis, based on all randomized subjects who received at least one drop of the study medication and had baseline cultures indicating pathogenic bacteria levels, unless otherwise indicated. If subjects were missing Visit 3 data, the last available on-treatment clinical and bacteriological data were to be carried forward.

Those intent-to-treat subjects who did not have a major protocol violation were included in the per-protocol population (PP). 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 as part of the sensitivity analyses.

**Determination of Sample Size**
Ninety-eight subjects with bacteriologically confirmed acute bacterial conjunctivitis, 49 subjects in each treatment group, were to participate in the study. Bacteriologically confirmed conjunctivitis was based on the pre-defined threshold criteria listed in the study protocol. The sample size was calculated based on a power of 0.80, and $\alpha \leq 0.05$ (two-sided, chi-square test comparing Vehicle with active treatment) and a microbial eradication rate of 89% in the active treatment group and a 64% eradication rate in the Vehicle group. The eradication rate estimates were based on the three most recent ophthalmic fluoroquinolones: moxifloxacin, gatifloxacin and levofloxacin. Subjects were recruited until the target sample size of 98 subjects with bacteriologically confirmed acute bacterial conjunctivitis was achieved.

### 3.1.3.2 Study #433

**Analysis of Primary Efficacy Endpoint**

The primary efficacy endpoints are:
- Clinical resolution, defined as the absence of both conjunctival discharge and bulbar conjunctival injection, after 5 days of treatment (Day 5 Visit);
- Microbial eradication, defined as the absence of all accepted ocular bacterial species that were present at or above threshold at baseline, after 5 days of treatment (Day 5 Visit).

For the primary efficacy endpoint of clinical resolution after 5 days of treatment the following hypotheses will be tested:

$$H_0: p_{ct} - p_{cv} \leq 0 \quad \text{vs} \quad H_1: p_{ct} - p_{cv} > 0$$

where $p_{ct}$ is the proportion of study eyes with clinical resolution at the Day 5 Visit for the 0.6% ISV-403 treatment group, and $p_{cv}$ is the proportion of study eyes with clinical resolution at the Day 5 Visit for the ISV-403 Vehicle treatment group.

For the primary efficacy endpoint of microbial eradication after 5 days of treatment the following hypotheses will be tested:

$$H_0: p_{mt} - p_{mv} \leq 0 \quad \text{vs} \quad H_1: p_{mt} - p_{mv} > 0$$

where $p_{mt}$ is the proportion of study eyes with microbial eradication at the Day 5 Visit for the 0.6% ISV-403 treatment group, and $p_{mv}$ is the proportion of study eyes with microbial eradication at the Day 5 Visit for the ISV-403 Vehicle treatment group.

For each of the primary efficacy endpoints, comparison between the 0.6% ISV-403 and ISV-403 Vehicle groups was performed using the Cochran-Mantel-Haenszel test, stratifying by center; and by a Pearson chi-squared test. Additionally, asymptotic normal theory was used to construct a 95% confidence interval for the difference between the percentages of subjects in the two treatment groups (calculated as percentage for 0.6% ISV-403 minus percentage for ISV-403 Vehicle) who attained a successful outcome (eradication; resolution).

**Analyses Sets**

The primary analysis set for the efficacy analysis will be the modified intent-to-treat (mITT) set. A secondary analysis of efficacy data will be performed on the true intent-to-treat (ITT) set. If major protocol violations should occur in 20 or more of the ITT set, efficacy analyses will also be performed for the per protocol (PP) set.

The Intent-to-Treat (ITT) analysis set will include all randomized subjects.

The modified Intent-to-Treat (mITT) analysis set will include all subjects in the ITT study population for whom baseline cultures indicated bacteria levels at or above threshold for any accepted ocular bacterial species.

The Per Protocol (PP) study population will include those subjects in the mITT analysis set who completed the study, and for whom no major protocol violations are noted. For the purpose of this determination, major protocol violations consist of:

- Subject was unmasked during the study;
- Any of the following deemed to affect study results:
  - Non-compliance with any scheduled study visit;
  - Non-compliance with study treatment;
  - Concomitant medications;
  - Non-compliance with study inclusion or exclusion criteria;
  - Non-compliance with study assessment procedures.

Analyses performed on the ITT set and mITT set will be according to treatments as randomized, and not according to treatments actually received, if these are different. Analyses performed on the PP set will be according to treatments actually received. In these analyses, only observed data will be employed.

**Determination of Sample Size**

Approximately 1100 subjects will be enrolled in this study to obtain approximately 380 subjects with bacteriologically confirmed acute bacterial conjunctivitis (190 in each treatment group), assuming a confirmation rate of around 35%. These 380 confirmed subjects are estimated to yield 170 evaluable subjects per treatment group, assuming a 10% dropout rate. Using a two-sided, alpha=0.05, chi-squared test, 170 subjects per treatment group yields:

- >90% power to detect a difference in the microbial eradication rate between active treatment and vehicle, assuming a microbial eradication rate of 90% in the active treatment group and 55% in the vehicle group.
- 90% power to detect a difference in the clinical resolution rate between active treatment and vehicle, assuming a clinical resolution rate of 33% in the active treatment group and 18% the vehicle group.

**3.1.3.3 Study #434**

**Analysis of Primary Efficacy Endpoint**

The primary efficacy endpoints are:

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

For the primary efficacy endpoint of clinical resolution after 5 days of treatment the following hypotheses will be tested:

$$H_0: p_{ct} - p_{ca} < -0.15 \quad \text{vs} \quad H_1: p_{ct} - p_{ca} \geq -0.15$$

where $p_{ct}$ is the proportion of study eyes with clinical resolution at the Day 5 Visit for the 0.6% ISV-403 treatment group, and $p_{ca}$ is the proportion of study eyes with clinical resolution at the Day 5 Visit for the Vigamox treatment group.

For the primary efficacy endpoint of microbial eradication after 5 days of treatment the following hypotheses will be tested:

$$H_0: p_{mt} - p_{ma} < -0.15 \quad \text{vs} \quad H_1: p_{mt} - p_{ma} \geq -0.15$$

where $p_{mt}$ is the proportion of study eyes with microbial eradication at the Day 5 Visit for the 0.6% ISV-403 treatment group, and $p_{ma}$ is the proportion of study eyes with microbial eradication at the Day 5 Visit for the Vigamox treatment group.

For each of the primary efficacy endpoints, summary tables were prepared indicating the number and percentage of subjects who presented each value of the binary response. Asymptotic normal

theory was used to construct a 95% confidence interval for the difference between the percentages of subjects in the two treatment groups (calculated as percentage for 0.6% ISV-403 minus percentage for Vigamox) who attained a successful outcome (eradication; resolution). Additionally, a comparison between the 0.6% ISV-403 and Vigamox groups was performed using the Cochran-Mantel-Haenszel test, stratifying by center; and by a Pearson chi-squared test.

**Analyses Sets**

The primary analysis set for the efficacy analysis will be the modified intent-to-treat (mITT) set. A secondary analysis of efficacy data will be performed on the true intent-to-treat (ITT) set. If major protocol violations should occur in 20 or more of the ITT sample, efficacy analyses will also be performed for the per protocol (PP) set.

The Intent-to-Treat (ITT) analysis set will include all randomized subjects.

The modified Intent-to-Treat (mITT) analysis set will include all subjects in the ITT study population for whom baseline cultures indicated bacteria levels at or above threshold for any accepted ocular bacterial species.

The Per Protocol (PP) study population will include those subjects in the mITT analysis set who completed the study, and for whom no major protocol violations are noted. For the purpose of this determination, major protocol violations consist of:

- Subject was unmasked during the study;
- Any of the following deemed to affect study results:
  - Non-compliance with any scheduled study visit;
  - Non-compliance with study treatment;
  - Concomitant medications;
  - Non-compliance with study inclusion or exclusion criteria;
  - Non-compliance with study assessment procedures.

Analyses performed on the ITT set and mITT set will be according to treatments as randomized, and not according to treatments actually received, if these are different. Analyses performed on the PP set will be according to treatments actually received. In these analyses, only observed data will be employed.

**Determination of Sample Size**

Approximately 1500 subjects will be enrolled in this study to obtain approximately 468 subjects with bacteriologically confirmed acute bacterial conjunctivitis (234 in each treatment group), assuming a confirmation rate of around 30%. These 468 confirmed subjects are estimated to yield 210 evaluable subjects per treatment group, assuming a 10% dropout rate. Using asymptotic normal theory to construct 95% confidence intervals, 210 subjects per treatment group yields:

- >90% power to conclude non-inferiority of 0.6% ISV-403 to Vigamox in the microbial eradication rate, using a 15% non-inferiority limit on the difference in microbial eradication (0.6% ISV-403 minus Vigamox) and assuming a microbial eradication rate of 90% in both treatment groups.

- 90% power to conclude non-inferiority of 0.6% ISV-403 to Vigamox in the clinical resolution rate, using a 15% non-inferiority limit on the difference in clinical resolution (0.6% ISV-403 minus Vigamox) and assuming a clinical resolution rate of 66% in both treatment groups.

**Statistical Reviewer's Comments:**
*For study #434, there is not a sufficient scientific justification for the 15% margin. The active comparator Vigamox (Moxifloxacin hydrochloride ophthalmic Solution, 0.5%) was approved in 2003. The original approval for Vigamox was based on one superiority study compared with a vehicle control, and one non-inferiority study compared with ocuflox ophthalmic solution. In the superiority trial, the clinical cure rate for patients who had baseline bacterial infection confirmed at end of therapy (Day 5) was 66% (95/143) for Vigamox, and 51% (74/144) for vehicle. The treatment difference was 15% with 95% confidence interval of (3.8%, 26.3%). With the effect size could be only 4% for the active control, a choice of 15% does not have any statistical reasoning. Therefore, there is lack of scientific basis for choosing 15% using Vigamox as the active comparator. Consequently, in study 434, the evidence of efficacy of besifloxacin compared to Vigamox cannot be meaningfully evaluated.*

### 3.1.4 Results and Conclusions

#### 3.1.4.1 Study #373

The efficacy results of clinical resolution and bacterial eradication at Visit 3 (Day 8 visit) are presents in the following table. The Cochran-Mantel-Haenszel (CMH) statistic stratifying by center was used to compare the ISV-403 and Vehicle groups with respect to the efficacy endpoints.

**Table 10: Efficacy Analysis Results for Study #373**

| | **Besifloxacin Suspension** n/N (%) | **Vehicle** n/N (%) | **p-value[1]** | **Difference (95% CI)** |
|---|---|---|---|---|
| **Clinical Resolution** | | | | |
| Clinical Resolution (mITT) | 37/60 (61.7%) | 20/56 (35.7%) | 0.0013 | 26% (8.4%, 43.5%) |
| **Bacterial Eradication** | | | | |
| Bacterial Eradication (mITT) | 54/60 (90%) | 38/55 (69.1%) | 0.0041 | 20.9% (6.5%, 35.3%) |

[1] p-value from CMH test stratified by center
Source: Sponsor's study #373 report Table 9.4.1-1 and 9.4.1-2

**Statistical Reviewer's Comments:**
*For the ITT Vehicle analysis set, two subjects were not included in the Sponsor's analysis because they withdrew early and had no follow-up visit after baseline visit. Additional sensitivity analysis was performed treating these two patients as treatment failure. In addition, Chi-square*

*test p-value is reported in the Reviewer's sensitivity analysis. The efficacy analysis results are listed in the following table.*

**Table 11: Statistical Reviewer's Efficacy Analysis Results for Study #373**

| | Besifloxacin Suspension n/N (%) | Vehicle n/N (%) | p-value[1] | Difference (95% CI) |
|---|---|---|---|---|
| **Clinical Resolution** | | | | |
| Clinical Resolution (mITT) | 37/60 (61.7%) | 20/58 (32.8%) | 0.0011 | 27.2% (9.8%, 44.5%) |
| **Bacterial Eradication** | | | | |
| Bacterial Eradication (mITT) | 53/60 (88.3%) | 38/58 (60.3%) | 0.0012 | 22.8% (8.1%, 37.5%) |

[1] p-value from Chi-square test

*Based on these results, besifloxacin ophthalmic suspension, 0.6% base, is statistically superior to vehicle in both clinical resolution and bacterial eradication rate.*

### 3.1.4.2 Study #433

The efficacy results of clinical resolution and bacterial eradication at Visit 2 (Day 5, ± 1 day) are presents in the following tables. Please note that fourteen (14) subjects randomized to the besifloxacin ophthalmic suspension treatment group received vehicle and 12 subjects randomized to vehicle received besifloxacin ophthalmic suspension. These subjects were differentiated in the primary analysis set by referring as either 'as treated' or 'as randomized'.

**Table 12: Study #433 Clinical Resolution at Visit 2, Study Eyes, mITT Population ('as randomized' and 'as treated')**

| | mITT Population ('as randomized') | | mITT Population ('as treated') | |
|---|---|---|---|---|
| | Besifloxacin Suspension (N=199) | Vehicle (N=191) | Besifloxacin Suspension (N=199) | Vehicle (N=191) |
| **Subjects with non-missing data** | 195 | 179 | 195 | 179 |
| **Clinical Resolution ('as observed')** | | | | |
| **Yes** | 90 (46.2%) | 63 (35.2%) | 89 (45.6%) | 64 (35.8%) |
| **No** | 105 (53.8%) | 116 (64.8%) | 106 (54.4%) | 115 (64.2%) |
| **p-value[1]** | 0.0104/0.0354 | | 0.0180/0.0584 | |
| **Difference (95% CI)[2]** | 11% (0.95%, 20.97%) | | 9.8% (-0.12%, 19.89%) | |
| **Subjects on Study with Missing Data** | 3 | 3 | 3 | 3 |

| | | | | |
|---|---|---|---|---|
| **Subjects Discontinued at or before Visit 2** | 1 | 9 | 1 | 9 |
| **Clinical Resolution (Missing or Discontinued Subjects Imputed as 'no'** | | | | |
| **Yes** | 90 (45.2%) | 63 (33.0%) | 89 (44.7%) | 64 (33.5%) |
| **No** | 109 (54.8%) | 128 (67.0%) | 110 (55.3%) | 127 (66.5%) |
| **p-value[1]** | 0.0084/0.0169 | | 0.0146/0.0292 | |
| **Difference (95% CI)[2]** | 12.2% (2.52%, 21.97%) | | 11.2% (1.49%, 20.94%) | |

[1] p-values from CMH test stratified by center / exact Pearson chi-square test, respectively.

[2] Difference calculated as besifloxacin minus vehicle. Positive values favor besifloxacin.

Source: Sponsor's study #433 report Table 9

**Table 13: Study #433 Microbial Eradication at Visit 2, Study Eyes, mITT Population ('as randomized' and 'as treated')**

| | **mITT Population ('as randomized')** | | **mITT Population ('as treated')** | |
|---|---|---|---|---|
| | **Besifloxacin Suspension (N=199)** | **Vehicle (N=191)** | **Besifloxacin Suspension (N=199)** | **Vehicle (N=191)** |
| **Subjects with non-missing data** | 194 | 173 | 194 | 173 |
| **Clinical Resolution ('as observed')** | | | | |
| **Yes** | 182 (93.8%) | 114 (65.9%) | 182 (93.8%) | 114 (65.9%) |
| **No** | 12 (6.2%) | 59 (34.1%) | 12 (6.2%) | 59 (34.1%) |
| **p-value[1]** | <0.0001 / < 0.0001 | | <0.0001 / <0.0001 | |
| **Difference (95% CI)[2]** | 27.9% (19.80%, 36.04%) | | 27.9% (19.80%, 36.04%) | |
| **Subjects on Study with Missing Data** | 4 | 9 | 4 | 9 |
| **Subjects Discontinued at or before Visit 2** | 1 | 9 | 1 | 9 |
| **Clinical Resolution (Missing or Discontinued Subjects Imputed as 'no'** | | | | |
| **Yes** | 182 (91.5%) | 114 (59.7%) | 182 (91.5%) | 114 (59.7%) |
| **No** | 17 (8.5%) | 77 (40.3%) | 17 (8.5%) | 77 (40.3%) |
| **p-value[1]** | <0.0001 / <0.0001 | | <0.0001 / <0.0001 | |
| **Difference (95% CI)[2]** | 31.8% (23.24%, 40.29%) | | 31.8% (23.25%, 40.29%) | |

[1] p-values from CMH test stratified by center / exact Pearson chi-square test, respectively.

[2] Difference calculated as besifloxacin minus vehicle. Positive values favor besifloxacin.

Source: Sponsor's study #433 report

**Statistical Reviewer's Comments:**
*Based on these results, for study #433, besifloxacin ophthalmic suspension, 0.6% base, is statistically superior to vehicle in both clinical resolution and bacterial eradication rate.*

### 3.1.4.2 Study #434

The efficacy results of clinical resolution and bacterial eradication at Visit 2 (Day 5, ± 1 day) are presents in the following tables. Please note that sixteen (16) subjects randomized to the besifloxacin ophthalmic suspension treatment group received Vigamox and 16 subjects randomized to Vigamox received besifloxacin ophthalmic suspension. These subjects were differentiated in the primary analysis set by referring as either 'as treated' or 'as randomized'.

**Table 14: Study #434 Clinical Resolution at Visit 2, Study Eyes, mITT Population ('as randomized' and 'as treated')**

| | **mITT Population ('as randomized')** | | **mITT Population ('as treated')** | |
|---|---|---|---|---|
| | **Besifloxacin Suspension (N=255)** | **Vehicle (N=278)** | **Besifloxacin Suspension (N=252)** | **Vehicle (N=281)** |
| **Subjects with non-missing data** | 251 | 274 | 248 | 277 |
| **Clinical Resolution ('as observed')** | | | | |
| **Yes** | 149 (59.4%) | 165 (60.2%) | 147 (59.3%) | 167 (60.3%) |
| **No** | 102 (40.6%) | 109 (39.8%) | 101 (40.7%) | 110 (39.7%) |
| **Difference (95% CI)[1]** | (-9.27%, 7.56%) | | (-9.43%, 7.41%) | |
| **Subjects on Study with Missing Data** | 0 | 1 | 0 | 1 |
| **Subjects Discontinued at or before Visit 2** | 4 | 3 | 4 | 3 |
| **Clinical Resolution (Missing or Discontinued Subjects Imputed as 'no'** | | | | |
| **Yes** | 149 (58.4%) | 165 (59.4%) | 147 (58.3%) | 167 (59.4%) |
| **No** | 106 (41.6%) | 113 (40.6%) | 105 (41.7%) | 114 (40.6%) |
| **Difference (95% CI)[1]** | (-9.30%, 7.46%) | | (-9.48%, 7.29%) | |

[1] Difference calculated as besifloxacin minus Vigamox. Positive values favor besifloxacin.
Source: Sponsor's study #434 report Table 8

**Table 15: Study #434 Microbial Eradication at Visit 2, Study Eyes, mITT Population ('as randomized' and 'as treated')**

| | mITT Population ('as randomized') | | mITT Population ('as treated') | |
|---|---|---|---|---|
| | Besifloxacin Suspension (N=255) | Vehicle (N=278) | Besifloxacin Suspension (N=252) | Vehicle (N=281) |
| **Subjects with non-missing data** | 249 | 267 | 245 | 271 |
| **Clinical Resolution ('as observed')** | | | | |
| **Yes** | 241 (96.8%) | 250 (93.6%) | 235 (95.9%) | 256 (94.5%) |
| **No** | 8 (3.2%) | 17 (6.4%) | 10 (4.1%) | 15 (5.5%) |
| **Difference (95% CI)[1]** | (-0.56%, 6.87%) | | (-2.27%, 5.17%) | |
| **Subjects on Study with Missing Data** | 2 | 8 | 3 | 7 |
| **Subjects Discontinued at or before Visit 2** | 4 | 3 | 4 | 3 |
| **Clinical Resolution (Missing or Discontinued Subjects Imputed as 'no'** | | | | |
| **Yes** | 241 (58.4%) | 250 (89.9%) | 235 (93.3%) | 256 (91.1%) |
| **No** | 14 (41.6%) | 28 (10.1%) | 17 (6.7%) | 25 (8.9%) |
| **Difference (95% CI)[1]** | (-0.01%, 9.17%) | | (-2.44%, 6.74%) | |

[1] Difference calculated as besifloxacin minus Vigamox. Positive values favor besifloxacin.
Source: Sponsor's study #434 report Table 9

**Statistical Reviewer's Comments:**

*For study #434, there is not a sufficient scientific justification for the 15% margin. The active comparator Vigamox (Moxifloxacin hydrochloride ophthalmic Solution, 0.5%) was approved in 2003. The original approval for Vigamox was based on one superiority study compared with a vehicle control, and one non-inferiority study compared with ocuflox ophthalmic solution. In the superiority trial, the clinical cure rate for patients who had baseline bacterial infection confirmed at end of therapy (Day 5) was 66% (95/143) for Vigamox, and 51% (74/144) for vehicle. The treatment difference was 15% with 95% confidence interval of (3.8%, 26.3%). With the effect size could be only 4% for the active control, a choice of 15% does not have any statistical reasoning. Therefore, there is lack of scientific basis for choosing 15% using Vigamox as the active comparator. Consequently, in study 434, the evidence of efficacy of besifloxacin compared to Vigamox cannot be meaningfully evaluated.*

## 3.2 Evaluation of Safety

The following tables summarized AEs for Study #373, #433, and #434 respectively.

**Table 16: Adverse events in >1% of subjects in either group for study #373**

| Adverse Event | Besifloxacin Suspension (n = 137) | Vehicle (n = 132) |
|---|---|---|
| Total Number of Adverse Event (1 or more) | 69 | 70 |
| Eye pain | 16 (11.7%) | 8 (6.1%) |
| Vision blurred | 15 (11.0%) | 13 (9.9%) |
| Eye irritation | 11 (8.0%) | 16 (12.1%) |
| Conjunctivitis bacterial | 9 (6.6%) | 15 (11.4%) |
| Conjunctivitis | 5 (3.7%) | 5 (3.8%) |
| Ocular hyperaemia | 4 (2.9%) | 6 (4.6%) |
| Conjunctival hyperaemia | 3 (2.2%) | 2 (1.5%) |
| Eye pruritus | 3 (2.2%) | 9 (6.8%) |
| Foreign body sensation | 3 (2.2%) | 1 (0.8%) |
| Conjunctivitis viral | 2 (1.5%) | 0 (0.0%) |
| Eye discharge | 2 (1.5%) | 3 (2.3%) |
| Eye disorder | 2 (1.5%) | 0 (0.0%) |
| Eyelid disorder | 2 (1.5%) | 1 (0.8%) |
| Eyelid margin crusting | 2 (1.5%) | 3 (2.3%) |
| Visual disturbance | 2 (1.5%) | 0 (0.0%) |
| Abnormal sensation in eye | 0 (0.0%) | 3 (2.3%) |
| Blepharitis | 0 (0.0%) | 2 (1.5%) |
| Eye swelling | 0 (0.0%) | 2 (1.5%) |
| Eyelid oedema | 0 (0.0%) | 3 (2.3%) |

Source: Sponsor's study #373 report Section 10.2 and Table 10.2-1

**Table 17: Adverse events in >1% of subjects in either group for study #433**

| Adverse Event | Besifloxacin Suspension (N = 741)[1] | Vehicle (N = 760) |
|---|---|---|
| Total Number of Adverse Events( AE) | 80 | 127 |
| Number of Eyes With at Least one AE | 68 (9.2%) | 106 (13.9%) |
| EYE DISORDERS | 68 (9.2%) | 106 (13.9%) |
| Conjunctivitis | 19 (2.6%) | 38 (5.0%) |
| Vision blurred | 9 (1.2%) | 17 (2.2%) |
| Conjunctivitis bacterial | 6 (0.8%) | 16 (2.1%) |
| Eye irritation | 8 (1.1%) | 3 (0.4%) |
| Eye pruritus | 9 (1.2%) | 2 (0.3%) |

[1] N= all treated eyes for the specified treatment group and includes study and fellow eyes
Source: Sponsor's study #433 report Table 21

**Table 18: Adverse events in >1% of subjects in either group for study #434**

| Adverse Event | Besifloxacin Suspension (N = 865) [1] | Vehicle (N = 855) |
|---|---|---|
| Total Number of Adverse Events( AE) | 135 | 153 |
| Number of Eyes With at Least one AE | 104 (12.0%) | 120 (14.0%) |
| EYE DISORDERS | 101 (11.7%) | 113 (13.2%) |
| Conjunctivitis | 24 (2.8%) | 33 (3.9%) |
| Conjunctivitis bacterial | 18 (2.1%) | 22 (2.6%) |
| Eye irritation | 3 (0.3%) | 12 (1.4%) |
| Eye pain | 5 (0.6%) | 9 (1.1%) |
| Vision blurred | 9 (1.0%) | 4 (0.5%) |

[1] N= all treated eyes for the specified treatment group and includes study and fellow eyes
Source: Sponsor's study #433 report Table 20

Please see the review of the medical officer for details of the safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The primary endpoints were analyzed by subgroups on age, gender, and race. In general, there were no marked differences in the efficacy results among the analysis subpopulations for all three studies.

**Table 19 Study #373 Analyses of Primary Endpoints by Age, Gender, and Race**

| | Clinical Resolution | | | | |
|---|---|---|---|---|---|
| | Besifloxacin Suspension (A) (N=60) Observed Response | | Vehicle (B) (N=58) Observed Response | | Observed Differences (A-B) |
| | n/m | % | n/m | % | % |
| **Gender** | | | | | |
| Male | 12/25 | 48.0 | 12/27 | 44.4 | 3.6 |
| Female | 25/35 | 71.4 | 7/31 | 22.6 | 48.8 |
| **Age** | | | | | |
| 0-11 | 13/16 | 81.3 | 6/12 | 50.0 | 31.3 |
| ≥ 12 | 24/44 | 54.6 | 13/46 | 28.7 | 25.9 |
| <65 | 35/55 | 63.6 | 18/51 | 35.3 | 28.3 |
| ≥ 65 years | 2/5 | 40.0 | 1/7 | 14.3 | 25.7 |
| **Race** | | | | | |
| Caucasian | 31/48 | 64.6 | 16/47 | 34.0 | 30.6 |
| Asian | 2/2 | 100.0 | n/a | n/a | n/a |
| African American | 0/1 | 0.0 | 3/6 | 50.0 | -50.0 |
| Hispanic | 5/8 | 62.5 | 0/2 | 0.0 | 62.5 |
| Other | 1/1 | 100.0 | 0/3 | 0.0 | 100.0 |

| Bacterial Eradication | | | | | |
|---|---|---|---|---|---|
| | Besifloxacin Suspension (A) (N=60) | | Vehicle (B) (N=58) | | |
| | Observed Response | | Observed Response | | Observed Differences (A-B) |
| | n/m | % | n/m | % | % |
| **Gender** | | | | | |
| Male | 23/25 | 92.0 | 16/27 | 59.3 | 32.7 |
| Female | 30/35 | 85.7 | 19/31 | 61.3 | 24.4 |
| **Age** | | | | | |
| 0-11 | 12/16 | 75.0 | 8/12 | 66.7 | 8.3 |
| ≥ 12 | 41/44 | 93.2 | 27/46 | 58.7 | 34.5 |
| <65 | 48/55 | 87.3 | 30/51 | 58.8 | 28.5 |
| ≥ 65 years | 5/5 | 100.0 | 5/7 | 71.4 | 28.6 |
| **Race** | | | | | |
| Caucasian | 43/48 | 89.6 | 29/47 | 61.7 | 27.9 |
| Asian | 2/2 | 100.0 | n/a | n/a | n/a |
| African American | 1/1 | 100.0 | 4/6 | 66.7 | 33.3 |
| Hispanic | 6/8 | 75.0 | 1/2 | 50.0 | 25.0 |
| Other | 1/1 | 100.0 | 1/3 | 33.3 | 66.7 |

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.

**Table 20 Study #433 Analyses of Primary Endpoints by Age, Gender, and Race**

| Clinical Resolution | | | | | |
|---|---|---|---|---|---|
| | Besifloxacin Suspension (A) (N=199) | | Vehicle (B) (N=191) | | |
| | Observed Response | | Observed Response | | Observed Differences (A-B) |
| | n/m | % | n/m | % | % |
| **Gender** | | | | | |
| Male | 35/75 | 46.7 | 27/78 | 34.6 | 12.1 |
| Female | 55/124 | 44.4 | 36/113 | 31.9 | 12.5 |
| **Age** | | | | | |
| 0-11 | 54/91 | 59.3 | 44/88 | 50.0 | 9.3 |
| ≥ 12 | 36/108 | 33.3 | 19/103 | 18.5 | 14.8 |
| <65 | 88/186 | 47.3 | 60/175 | 34.3 | 13.0 |
| ≥ 65 years | 2/13 | 15.4 | 3/16 | 18.8 | -3.4 |
| **Race** | | | | | |
| Caucasian | 58/125 | 46.4 | 42/126 | 33.3 | 13.1 |
| Asian | 3/3 | 100.0 | 3/5 | 60.0 | 40.0 |
| African American | 8/18 | 44.4 | 6/18 | 33.3 | 11.1 |
| Other | 21/53 | 39.6 | 12/42 | 28.6 | 11.0 |

| Bacterial Eradication | | | | | |
|---|---|---|---|---|---|
| | Besifloxacin Suspension (A) (N=199) Observed Response | | Vehicle (B) (N=191) Observed Response | | Observed Differences (A-B) |
| | n/m | % | n/m | % | % |
| **Gender** | | | | | |
| Male | 67/75 | 89.3 | 43/78 | 55.1 | 34.2 |
| Female | 115/124 | 92.7 | 71/113 | 62.8 | 29.9 |
| **Age** | | | | | |
| 0-11 | 76/91 | 83.5 | 47/88 | 53.4 | 30.1 |
| ≥ 12 | 106/108 | 98.2 | 67/103 | 65.1 | 33.1 |
| <65 | 169/186 | 90.9 | 105/175 | 60.0 | 30.9 |
| ≥ 65 years | 13/13 | 100.0 | 9/16 | 56.3 | 43.7 |
| **Race** | | | | | |
| Caucasian | 118/125 | 94.4 | 75/126 | 59.5 | 34.9 |
| Asian | 3/3 | 100.0 | 2/5 | 40.0 | 60.0 |
| African American | 18/18 | 100.0 | 15/18 | 83.3 | 16.7 |
| Other | 43/53 | 81.1 | 22/42 | 52.4 | 28.7 |

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.

**Table 21 Study #434 Analyses of Primary Endpoints by Age, Gender, and Race**

| Clinical Resolution | | | | | |
|---|---|---|---|---|---|
| | Besifloxacin Suspension (A) (N=255) Observed Response | | Vigamox (B) (N=278) Observed Response | | Observed Differences (A-B) |
| | n/m | % | n/m | % | % |
| **Gender** | | | | | |
| Male | 64/111 | 57.7 | 83/137 | 60.6 | -2.9 |
| Female | 85/144 | 59.0 | 82/141 | 58.2 | 0.8 |
| **Age** | | | | | |
| 0-11 | 64/84 | 76.2 | 57/73 | 78.1 | -1.9 |
| ≥ 12 | 85/171 | 49.7 | 108/205 | 52.7 | -3.0 |
| <65 | 132/219 | 60.3 | 135/212 | 63.7 | -3.4 |
| ≥ 65 years | 17/36 | 47.2 | 30/66 | 45.5 | 1.7 |
| **Race** | | | | | |
| Caucasian | 101/178 | 56.7 | 112/195 | 57.4 | -0.7 |
| Asian | 21/34 | 61.8 | 27/44 | 61.4 | 0.4 |
| African American | 16/29 | 55.2 | 16/25 | 64.0 | -8.8 |
| Other | 11/14 | 78.6 | 10/14 | 71.4 | 7.2 |

| Bacterial Eradication | | | | | |
|---|---|---|---|---|---|
| | Besifloxacin Suspension (A) (N=255) Observed Response | | Vigamox (B) (N=278) Observed Response | | Observed Differences (A-B) |
| | n/m | % | n/m | % | % |
| **Gender** | | | | | |
| Male | 100/111 | 90.1 | 126/137 | 92.0 | -1.9 |
| Female | 141/144 | 97.9 | 124/141 | 87.9 | 10.0 |
| **Age** | | | | | |
| 0-11 | 79/84 | 94.1 | 63/73 | 86.3 | 7.8 |
| ≥ 12 | 162/171 | 94.7 | 187/205 | 91.2 | 3.5 |
| <65 | 207/219 | 94.5 | 190/212 | 89.6 | 4.9 |
| ≥ 65 years | 34/36 | 94.4 | 60/66 | 90.9 | 3.5 |
| **Race** | | | | | |
| Caucasian | 169/178 | 94.9 | 181/195 | 92.8 | 2.1 |
| Asian | 34/34 | 100.0 | 38/44 | 86.4 | 13.6 |
| African American | 25/29 | 86.2 | 19/25 | 76.0 | 10.2 |
| Other | 13/14 | 92.9 | 12/14 | 85.7 | 7.2 |

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

There is one major statistical issue for this submission: the choice of non-inferiority margin for the non-inferiority study #434.

For study #434, a non-inferiority margin of 15% was used. The margin was recommended to the sponsor by the FDA clinical review team.

However, there is not a sufficient scientific justification for the 15% margin. The active comparator Vigamox (Moxifloxacin hydrochloride ophthalmic Solution, 0.5%) was approved in 2003. The original approval for Vigamox was based on one superiority study compared with a vehicle control, and one non-inferiority study compared with ocuflox ophthalmic solution. In the superiority trial, the clinical cure rate for patients who had baseline bacterial infection confirmed at end of therapy (Day 5) was 66% (95/143) for Vigamox, and 51% (74/144) for vehicle. The treatment difference was 15% with 95% confidence interval of (3.8%, 26.3%). With the effect size could be only 4% for the active control, a choice of 15% does not have any statistical reasoning. Therefore, there is lack of scientific basis for choosing 15% using Vigamox as the active comparator. Consequently, in study 434, the evidence of efficacy of besifloxacin compared to Vigamox cannot be meaningfully evaluated.

In study #373, at Visit 3 (Day 8, +1 day), the clinical resolution rate for besifloxacin hydrochloride ophthalmic suspension, 0.6% as base vs. Vehicle was 61.7% vs. 35.7%, a 26% treatment difference with 95% confidence interval of (8.4%, 43.5%); and for the bacterial eradication rate was 90.0% vs. 69.1%, a 20.9% treatment difference with 95% CI of (6.5%, 35.3%).

In study #433, at Visit 2 (Day 5, ±1 day), the clinical resolution rate for besifloxacin hydrochloride ophthalmic suspension, 0.6% as base vs. Vehicle was 45.2% vs. 33.0%, a 12.2% treatment difference with 95% confidence interval of (2.5%, 22.0%); and the bacterial eradication rate was 91.5% vs. 59.7%, a 31.8% treatment difference with 95% CI of (23.2%, 40.3%). The study results demonstrated statistically superior to vehicle in both clinical resolution and eradication of baseline bacterial infection at Visit 2 (Day 5, ±1 day).

## 5.2 Conclusions and Recommendations

For the non-inferiority study #434, there is lack of clinical and statistical basis for choosing a non-inferiority margin of 15% in a non-inferiority trial using Vigamox as the active comparator for the treatment of bacterial conjunctivitis. Consequently, the evidence of efficacy of Besifloxacin suspension in study #434 cannot be evaluated through the claim of non-inferiority of Besifloxacin suspension to Vigamox using a margin of 15%.

In study #373, the study results demonstrated that besifloxacin hydrochloride ophthalmic suspension, 0.6% as base, was statistically superior to vehicle in both clinical resolution and eradication of baseline bacterial infection at Visit 3 (Day 8, +1 day).

In study #433, the study results demonstrated that besifloxacin hydrochloride ophthalmic suspension, 0.6% as base was statistically superior to vehicle in both clinical resolution and eradication of baseline bacterial infection at Visit 2 (Day 5, ±1 day).

In conclusion, from the results of both study #373 and study #433, this submission provided adequate statistical evidence that besifloxacin hydrochloride ophthalmic suspension (0.6% as base) is superior to vehicle for the treatment of bacterial conjunctivitis. However, we do not recommend reporting the results of the non-inferiority study #434 in the labeling since the evidence of efficacy of Besifloxacin suspension in study #434 cannot be evaluated through the claim of non-inferiority compared to Vigamox using a margin of 15%.

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