DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH

Dermatologic and Ophthalmic Drugs

Advisory Committee

Session 1

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C O N T E N T S

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M. Roy Wilson, M.D., M.S.

FDA MEMBERS (Non-Voting):

Edward M. Cox, M.D., M.P.H.
Wiley Chambers, M.D.
Martin Nevitt, M.D., M.P.H.

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. REPKA: Good morning. I am Michael Repka, chairman of this panel, which will this morning be discussing the new drug application 22-308, besifloxacin ophthalmic solution, proposed for the treatment of bacterial conjunctivitis.

Introduction of Committee

DR. REPKA: Before beginning with those proposals, we are going to start with introductions of the committee. I think we will start with Dr. Strahlman, to my right.

DR. STRAHLMAN: Hello. I am Ellen Strahlman. I am the chief medical officer for GlaxoSmithKline and I am the industry representative on the panel.

DR. GATES: William Gates, Nashville, Tennessee, private practice.

DR. MILLER: Dr. Marijean Miller. I am an attending physician at Children's National Medical Center and an associate professor at George Washington University.

DR. WILSON: M. Roy Wilson, chancellor, Colorado Denver. I am a professor of ophthalmology.

DR. MAJUMDER: Mary Majumder. I am at the Center for Medical Ethics and Health Policy at Baylor College of Medicine, and I am here as the consumer representative.

DR. BILKER: Warren Bilker. I am a professor of biostatistics at the University of Pennsylvania.

DR. AFSHARI: Natalie Afshari, associate professor of ophthalmology in cornea and refractive surgery at Duke University.

MS. COFER: Paula Cofer, FDA patient representative.

DR. LAVIN: Philip Lavin, biostatistician with Averion.

DR. NEVITT: I am Martin Nevitt, medical officer with the FDA in the Division of Anti-Infective and Ophthalmology Products.

DR. CHAMBERS: Wiley Chambers, Acting Director, Division of Anti-Infective and Ophthalmology Products, FDA.

DR. COX: Ed Cox, Director of the Office of Antimicrobial Products, CDER, FDA.

DR. REPKA: Great, thank you. I am Michael Repka, professor of ophthalmology and pediatrics at Johns Hopkins University, in Baltimore.

For topics such as those being discussed at today's meeting there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. A press conference will be held immediately following the meeting today.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Conflict of Interest Statement

DR. WAPLES: The Food and Drug Administration is convening today's meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest of laws, covered by, but not limited to those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws under 18 U.S.C. Section 208. Congress has authorized FDA to grant waivers to special government employees and regular federal

employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consultants, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves the drug application NDA 22-308, besifloxacin ophthalmic solution, sponsored by Bausch & Lomb, Inc., proposed for the treatment of bacterial

conjunctivitis. This is a particular matters meeting during which specific matters related to Bausch & Lomb's besifloxacin ophthalmic suspension will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Ellen Strahlman is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Her role at this meeting is to represent industry in general and not any particular company. Dr. Strahlman is employed by GlaxoSmithKline.

We would like to remind members and temporary voting members that if the discussions involve any other products of firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise

the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. REPKA: Thank you for that. I think we will move now to some introductory comments by Dr. Wiley Chambers, Acting Director, Division of Anti-Infective and Ophthalmic Products.

FDA Introductory Remarks

DR. CHAMBERS: Thank you. On behalf of the FDA, I would like to welcome everyone to the meeting and thank you very much for taking the time out of your schedules to come and provide advice to us.

In the past, certainly within the ophthalmic products, we have tended to have relatively few meetings not to discuss most new drug applications that came to the agency but only bring you things that were particularly controversial or brand-new indications. With the passage of the FDA Amendments Act, there was a requirement, or at least discussion in there and a change basically in policy where we assume that we will bring all molecular entity products to the advisory committee whether there are controversies or not, whether it is a new indication or not, and general encouragement to bring more topics to advisory committees.

So, some of you have already seen an increase in the number of meetings we have. We are still going to try and keep them as efficient as possible, and we will take whatever time is necessary to fully discuss the topics but we won't otherwise try and drag things out.

Today we have two topics so we will do one in the morning and one in the afternoon. We are trying to focus the discussions for you generally on clinical topics because that is generally where the expertise around the table is. That does not mean that if you are aware of anything related to the product that you are not free to discuss that, explore it, whatever. Feel free to not limit your remarks to just a particular clinical area because that is what we happen to bring up.

We have relatively few questions. It is not that the questions are not important but the discussion is at least as important about any of the particular topics. So, we welcome a full discussion and we are very interested in the comments that you make in addition to just voting on particular questions.

Even if the committee thinks the product is great, for lack of a better term, it does not mean that we will

necessarily approve the product tomorrow. There are other parts of the application that we will not necessarily be discussing.

They include things like chemistry, manufacturing, other facilities, other aspects within the application. Those all still under review for each of the two different applications that we are talking about, and we will continue to complete them in due course. What we are trying to bring to you are the particular things that we thought need a fuller discussion, particularly in public. But, again, any kind of questions are fair game and any discussion is fair game. I, again, thank you for taking the time to come.

DR. REPKA: Thank you, Dr. Chambers. We will now proceed with our guest speaker presentation. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Industry Presentation

Introduction and Presentation

DR. WEET: Dr. Repka, Dr. Cox, Dr. Chambers, committee members, FDA staff and guests, good morning.

[Slide]

On behalf of Bausch & Lomb, I would like to thank the Division and the Dermatologic and Ophthalmic Advisory Committee for the opportunity to present and discuss with you our NDA for besifloxacin ophthalmic suspension, 0.6 percent.

[Slide]

I am Jack Weet, and I will be giving you brief background information on besifloxacin ophthalmic suspension and our development program.

[Slide]

Besifloxacin was specifically formulated for ophthalmic use for the treatment of bacterial conjunctivitis. Of note, besifloxacin is a new chemical entity and is being brought to you for your review today under the provisions of FDAAA, a relatively new statute which requires advisory committee review of all new chemical entities.

[Slide]

Besifloxacin is the only fluoroquinolone that has been developed exclusively for ophthalmic use. It has not been previously commercialized in any systemic product. Its proposed 0.6 percent suspension formulation has been

specifically designed for the treatment of conjunctivitis.

[Slide]

The reason we are here today is because bacterial conjunctivitis is a common ocular disorder that affects people of all ages. Bausch & Lomb believes that besifloxacin ophthalmic suspension will provide an important addition to the treatment options available to doctors and their patients for the treatment of this disease.

The data from our clinical trials will show that besifloxacin offers broad-spectrum bactericidal activity. It results in statistically significant microbial eradication and clinical resolution. It has a favorable safety profile and a convenient dosing regimen. Importantly, besifloxacin ophthalmic suspension is appropriate for treating patients as young as one year old.

[Slide]

The besifloxacin development program includes more than five years of research, involving more than 2,600 patients in eight studies. These include 2,600 patients in healthy volunteers. Based on FDA feedback, we initiated study 373, a double-masked, placebo-controlled trial, to provide endpoint information for subsequent studies.

By the end of 2005, we received feedback from the division on our Phase 2 trial, and gained concurrence to proceed with two Phase 3 trials, study 433 and 434. Nonclinical toxicology and chemical information was pre-submitted to the division in December of 2007, and the remainder of the NDA was submitted to the division in 2008. The application will be granted an action next year, which brings us to today.

[Slide]

Our speakers today will present information on the background of the disease, further information on the development program, and data supporting the safety and efficacy of besifloxacin.

[Slide]

At this point I would like to turn the podium over to Dr. Susan Schneider for discussion of the disease background. Dr. Schneider?

Disease Background

DR. SCHNEIDER: Good morning.

[Slide]

My name is Susan Schneider, and I will be presenting a brief overview of bacterial conjunctivitis.

First, I will be describing characteristics of bacterial conjunctivitis. Next, I will speak about pathogens that cause this disease, and then review current treatment.

[Slide]

Conjunctivitis is a common ocular disease that probably almost everyone here today has some experience with. Bacterial conjunctivitis affects the surface of the eye including the mucous membranes surrounding the eye. This type of infection is prevalent among children and the elderly.

Another significant attribute of this disease is that it is contagious. It can be transmitted via hand to eye contact; by cross-contamination from one eye to another; and through contaminated materials that are shared. This can be particularly problematic in school, family and work settings where close contact is unavoidable.

Prevalence has been reported to be as high as five million cases per year in the United States. Up to one percent of all primary care consultations involve bacterial conjunctivitis.

[Slide]

One reason that conjunctivitis is so common is that the causative pathogens usually inhabit normal skin and respiratory microflora. Four causative pathogens tend to be the most prevalent in this disease. They are Haemophilous influenzae, a gram-negative organism, and Strep. pneumoniae, Staph. aureus and Staph. epidermidis, all gram-positive organisms.

Many other pathogens can also cause bacterial conjunctivitis including gram-positive organisms such as viridans strep. and corynebacteria, and gram-negatives such as moraxella.

Differences exist in the relative prevalence of pathogens depending on patient age and the prevalence and drug susceptibility of these pathogens can vary based on a number of social and environmental factors.

[Slide]

Although conjunctivitis is almost exclusively a community-acquired disease, multiple studies over the last 10-15 years have reported an increase in drug-resistant and even multi-drug-resistant organisms. For example, this study, published earlier this year, included a retrospective analysis of more than 1,200 bacterial conjunctivitis

isolates recovered over a ten-year period at the Bascom Palmer Eye Institute.

The authors noted a remarkably steady trend of increasing prevalence of methicillin-resistant Staph. aureus or MRSA within that overall Staph. aureus population. As many in this audience are well aware, MRSA is highly correlated with resistance to multiple, otherwise safe and effective, antibacterial agents.

[Slide]

Conjunctivitis is usually self-limiting but on occasion it can progress to a more serious ocular disease. The standard of care for conjunctivitis is topical treatment with broad-spectrum, ideally bactericidal agents.

From the perspective of patients, their families and healthcare providers, benefits include accelerated symptomatic relief, eradication of causative pathogens and remission of the disease. From an epidemiologic perspective, treatment with effective topical agents reduces the rate of reinfection and the spread of infection to others.

[Slide]

With this disease background in mind, let's now

take a look at the attributes that clinicians and patients might like to see in a new product to treat bacterial conjunctivitis. First, since numerous pathogens can cause bacterial conjunctivitis, treatment is empiric so a broad-spectrum therapy would be preferred.

It would be active against prevalent organisms. The treatment would be bactericidal. It would exhibit reduced potential for development of resistance. The treatment would be safe, with a very low incidence of adverse events. The dosing regimen would be convenient and simple. We would also see sustained dwell time on the surface of the eye where the disease process is ongoing. Finally, we would have a drug that is specifically designed to treat a local ocular disease.

[Slide]

In conclusion, conjunctivitis is a common, contagious eye disease in which drug resistance is becoming increasingly prevalent. The standard of care is empiric treatment with a topical broad-spectrum bactericidal therapy which provides clinical remission, reduction of spread and reinfection, and eradication of causative pathogens.

As the treatment of conjunctivitis continues to

evolve, we have focused the development of besifloxacin ophthalmic suspension on addressing the need for a new localized ocular therapy.

With this background in mind, I would now like to invite Dr. Timothy Morris to present the nonclinical microbiology of besifloxacin. Thank you.

Nonclinical Microbiology

DR. MORRIS: Good morning. I am Timothy Morris with Bausch & Lomb microbiology.

[Slide]

Today I will present a brief overview of the nonclinical besifloxacin microbiology studies. Besifloxacin is a novel fluoroquinolone. It has broad-spectrum bactericidal activity against ocular pathogens, including multi-resistant isolates that are prevalent in today's clinical settings.

I will describe the balanced dual targeting properties of besifloxacin, and then I will explain how those properties are consistent with the low incidence of resistance development that has been observed.

[Slide]

Besifloxacin is a fluoroquinolone so for some

members of this audience the core structure should be familiar. What makes besifloxacin structurally unique are the substituents at the C7 and the C8 positions. These substituents drive besifloxacin's broad-spectrum potency and activity against ocular pathogens.

From nonclinical studies we have concluded that besifloxacin's mode of action is consistent with that of other fluoroquinolones. By that, I mean that besifloxacin kills bacteria by simultaneously inhibiting not one but two essential bacterial enzymes, DNA gyrase and topoisomerase IV.

[Slide]

In the next few slides I will be presenting bacterial activity testing of besifloxacin. So, first I would like to define some key terms.

MIC is the minimum inhibitory concentration to inhibit growth of a single bacterial isolate. MIC-90 is concentration to inhibit growth of at least 90 percent of at least 10 separate isolates. MBC is the minimum bactericidal concentration required to kill at least 99.9 percent of treated bacterial cells.

One of the ways to express the bactericidal

activity of an anti-infective drug is to express it as the MBC:MIC ratio. So, for prospective agents with MBC:MIC ratios less than or equal to 4 for the majority of isolates are considered bactericidal. Whereas, agents that have ratios that are greater than or equal to 8 for the majority of isolates would be considered bacteriostatic.

[Slide]

On this slide we will show the relative potency of besifloxacin compared to moxifloxacin for Staphylococcus aureus and epidermidis. Since this is the first slide presenting MIC data, I would like to explain how these slides are organized.

The scale at the bottom will show the range of test concentrations for these MIC studies. As the dotted lines show, the test concentrations ranged from 0.008 up to 8 ug/mL, which is a 1000-fold range of MIC values. As the arrows show, the most potent MIC values are to the left and the least potent MIC values will be to the right. The range of MIC values for besifloxacin will be shown as orange bars and the range of MIC values for moxifloxacin will be shown as blue bars. The downward yellow triangles will indicate MIC-90 values for each test agent.

Because breakpoints are not defined for topical ophthalmics, in vitro activity testing for these agents relies on MIC breakpoints from systemic antibacterials simply to define individual isolates as either susceptible or resistant.

The first two bars summarize MIC data for all phenotypes of Staphylococcus aureus in this study. Based on a four-fold difference in MIC-90s, besifloxacin was more potent than moxifloxacin, and this trend was evident for both quinolone-resistant as well as quinolone-susceptible subsets.

Again, we see very similar trends for Staphylococcus epidermidis. Recall that these are two organisms that show increasing prevalence of drug resistance in ocular settings.

[Slide]

On this slide we again see lower MIC values for besifloxacin compared with moxifloxacin for other gram-positive ocular pathogens. The pattern of improved potency relative to moxifloxacin is particularly notable in all isolates of Streptococcus pneumoniae, including both quinolone-sensitive and quinolone-resistant subsets.

Although not shown here, besifloxacin is also equally active against penicillin-resistant as well as penicillin-sensitive Streptococcus pneumoniae.

[Slide]

Moving on to the most prevalent gram-negative ocular pathogens, besifloxacin and moxifloxacin demonstrate comparable MICs regardless of the presence or absence of beta-lactamase.

[Slide]

As shown here in gold text, besifloxacin has, thus, demonstrated activity against the most prevalent conjunctivitis pathogens. Besifloxacin also shows potent broad-spectrum activity against a variety of other gram-positive and gram-negative ocular pathogens. That observed activity is better than or comparable to that of other ophthalmic antibacterials. Finally, besifloxacin remains highly active against a variety of resistant organisms.

[Slide]

This slide summarizes the bactericidal activity of besifloxacin against recent ocular isolates of the 4 most prevalent conjunctivitis pathogens. Over 80 percent of the 40 Haemophilous influenzae isolates showed MBC:MIC ratios

that were less than or equal to 2, indicating highly bactericidal activity.

Similar trends were also observed for Streptococcus pneumoniae, Staphylococcus aureus and Staphylococcus epidermidis. Note that each of these test sets included representative drug-resistant isolates. Finally, besifloxacin was the only agent to give measurable MICs and MBCs for 100 percent of the test isolates in this study.

[Slide]

So, the favorable antibacterial properties of besifloxacin are related to its mechanism of action. Bacteria develop high-level fluoroquinolone resistance principally through mutations in two target enzymes. Thus, high-level resistance to besifloxacin requires mutations in more than one target.

As I have already shown, besifloxacin retains higher potency against organisms that are resistant to early generation fluoroquinolones. Besifloxacin also demonstrates low rates of spontaneous resistance development.

[Slide]

Now let's take a look at the data that support

those conclusions. This slide summarizes besifloxacin inhibition of purified bacterial DNA gyrase and topoisomerase IV enzymes. Besifloxacin shows the best potency as measured by IC-50 values against both Streptococcus pneumoniae enzyme targets.

Also, based on IC-50 ratios, highlighted here in the blue box, besifloxacin shows the most balanced activity of these three quinolones.

Here are the corresponding data from the reference organism E. coli. The absolute potency of all three agents is similar, however, as indicated by the IC-50 ratios again in the blue box, the relative balance of besifloxacin activity against gyrase and topoisomerase IV is improved.

Although not shown here, besifloxacin dual targeting was further demonstrated by cleavable complex assays against the same two bacterial enzymes.

[Slide]

Another advantage of balanced dual targeting is that this property correlates with lower rates of spontaneous resistance development. In fact, no quinolone-resistant strains emerged after besifloxacin treatment of 656 conjunctivitis isolates in the besifloxacin clinical

efficacy studies.

In nonclinical resistance studies, where much larger populations of bacteria were exposed to test agents, lower frequencies of resistant variants were observed with besifloxacin. As you can see with Staphylococcus aureus and Streptococcus pneumoniae data besifloxacin had the lowest resistance development when compared with ciprofloxacin and moxifloxacin. In contrast to both comparator quinolones, no viable mutants were recovered on plates containing besifloxacin concentrations at four-fold above the MIC.

[Slide]

In summary, the nonclinical antibacterial activity studies demonstrate that besifloxacin is a novel, broad-spectrum fluoroquinolone with relatively balanced dual targeting activity. It provides potent bactericidal activity against prevalent ocular pathogens, and that activity is particularly evident against resistant isolates, including highly fluoroquinolone-resistant strains.

Lower rates of spontaneous resistance development have been observed in nonclinical studies, and no quinolone resistance development was observed in clinical efficacy studies. Therefore, the antibacterial profile of

besifloxacin is well suited for empiric treatment of bacterial conjunctivitis.

[Slide]

Now, if there are no clarifying questions, Dr. Comstock will present results from clinical pharmacokinetics and efficacy studies. Thank you.

Efficacy

DR. COMSTOCK: Good morning. My name is Tim Comstock, Bausch & Lomb, and I will be presenting the efficacy data generated during our clinical development program.

[Slide]

I will first present two slides to give you a quick overview of the clinical development program, and then I will present the three safety and efficacy studies that form the basis of our efficacy conclusions. The presentation of these studies will focus on the primary efficacy endpoints, clinical resolution and bacterial eradication. Finally, I will conclude with an overview of the integrated clinical microbiology data from these same three studies.

[Slide]

The development program consisted of eight trials. This discussion will focus on the four trials highlighted in this slide. First I would like to give you a brief overview of the rationale for using the 0.6 percent concentration that was evaluated in each of these efficacy studies.

[Slide]

Prior to starting our clinical studies our preclinical testing, with dosing which ranged from 0.1 percent to 0.6 percent, demonstrated dose-dependent conjunctival drug concentrations in animals. From that data we modeled three times daily dosing and evaluated PK parameters, C-max and area under the curve relative to the MICs necessary for treating a variety of pathogens known to be associated with this condition.

From this analysis, it was predicted that the 0.6 percent TID regimen would meet the target values that have been associated with antimicrobial efficacy for fluoroquinolones. Therefore, the data that I will present today were obtained following treatment with the 0.6 percent besifloxacin formulation.

[Slide]

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Study number 424 was conducted in healthy human volunteers to measure tear concentrations of besifloxacin after a single administration of the 0.6 percent formulation. The study confirmed that therapeutic drug levels were achieved in human tears, which is a relevant site for evaluating a drug to treat ocular surface infections.

The maximum levels achieved in tears were at least 600-fold higher than the MIC-90s for some organisms that are most prevalent in bacterial conjunctivitis infections. In fact, 24 hours after a single dose of the 0.6 formulation 1.6 ug/g were present in the tears.

[Slide]

So, I will now turn to the clinical studies that form the basis of our efficacy conclusions. This slide highlights similarities and differences between the three studies that I am about to describe. Each of these studies lasted for eight days. All studies evaluated five days of three times daily dosing of the medications that were being tested. All of the studies had three visits at which a standard battery of ophthalmic tests were performed, including the collection of conjunctival cultures.

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Visit 2 differed between the studies. In study 373, the date for visit 2 was day four, plus/minus one day, and in the other two studies the date for visit 2 was day five, plus/minus one day.

[Slide]

Several populations were evaluated in each of the analyses. I will be talking primarily about the culture confirmed population which consists of those patients who had conjunctivitis severity that met the inclusion criteria at baseline and also had cultures at baseline that confirmed the bacterial nature of the conjunctivitis.

[Slide]

In each study that I am about to discuss one eye of each patient was identified as the study eye for the clinical efficacy analysis. The study eye was the eye that had a culture confirmed bacterial conjunctivitis and had the most severe conjunctivitis according to the cumulative severity grade of the indices used to evaluate clinical resolution.

[Slide]

In all studies that included bulbar conjunctival injection and discharge from the conjunctiva. In one study

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it also included palpebral injection. It was possible for a fellow eye to contribute data to the microbiological data at the species level. That could happen when a fellow eye met all of the inclusion criteria, was not the eye with the most severe conjunctivitis and the infecting agent was different than the species that was measured in the study eye.

So, in no case did the same organism from each eye of a patient contribute to these data, but in some cases each eye may have contributed a different organism to that data set.

[Slide]

Pivotal study 373 is the first that I will discuss. Study 373 was a little different from the other studies because the primary efficacy endpoint was at visit 3, on day eight. In this study visit 2 took place at day four rather than day five as in the two other studies.

We also, in this study, used three clinical signs of conjunctivitis to determine resolution of the condition. These were conjunctival discharge, bulbar injection which was used in all three of the studies, and palpebral injection which was only used in this study. Microbial eradication was defined as the absence of the ocular

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bacterial species that were present at baseline at or above threshold levels.

[Slide]

The study included 35 sites and 269 patients were randomized and 44 percent of those had positive baseline cultures, and they formed the basis of the analysis that I will describe.

[Slide]

There is a wide range of ages included in all of these studies. The study included primarily whites, primarily females and, most importantly, balanced demographics between the two study groups. This demographic is representative of the U.S. population as a whole and is what one would expect in a study of bacterial conjunctivitis.

[Slide]

The range of organisms encountered during study 373 was also what we would expect in any study of bacterial conjunctivitis. In fact, you will see that the top four pathogens encountered are the same in each of the three main efficacy trials.

[Slide]

This graph shows the statistically significant difference in clinical resolution between besifloxacin and the vehicle at the primary efficacy visit on day eight. I am going to show you several graphs designed this same way. So, to orient you for future graphs I will spend a little more time on this one.

On the Y axis is the proportion of patients who met whichever endpoint we are talking about. In this case we are presenting clinical resolution, but you will see similar graphs for microbial eradication. On the X axis are the visits at which these endpoints were evaluated, in this case day four and day eight. The primary efficacy in each of these analyses will be highlighted with the dark background, and the p values will be indicated for each of the visits.

As shown here, in study 373, the difference in clinical resolution following treatment with besifloxacin compared with vehicle was statistically significant at visit 3, the primary efficacy endpoint.

[Slide]

To determine clinical resolution of conjunctivitis we thought it was appropriate to provide this analysis so

you can do a better apples to apples comparison between the three studies. Using only two signs of clinical resolution, the rates of resolution for both besifloxacin and the vehicle shifted upwards. A higher proportion of patients had clinical resolution when palpebral conjunctival injection was not considered. However, a statistically significant difference remained at visit 3, the primary endpoint.

[Slide]

Here you can see the significantly higher microbial eradication rate with besifloxacin versus its vehicle at the primary efficacy visit on day eight, and also a significant difference on day four.

[Slide]

Species specific eradication data shows the broad-spectrum antimicrobial nature of besifloxacin. There is a high rate of eradication of the more frequently encountered causative organisms regardless of their gram-stain characteristics.

[Slide]

In study 373 clinical resolution and microbial eradication were statistically superior at visit 3 with

besifloxacin treatment compared with its vehicle, meeting the primary endpoints. This was true whether the data were analyzed using three or two indices of clinical resolution.

[Slide]

I will now talk about pivotal study 433. There are two differences in 433 relative to study 373 that are important. In study 433 it was the absence of two signs of conjunctivitis, conjunctival bulbar injection and conjunctival discharge. They were evaluated to determine the clinical resolution.

The other difference was that visit 2 rather than visit 3 was the primary efficacy endpoint. In the previous study visit 2 took place on day four. In this study visit 2 took place on day five.

[Slide]

This was a much larger study than the previous study. In this study 58 sites participated. Nearly 1,000 patients were enrolled and 41 percent of these had culture confirmed bacterial conjunctivitis.

[Slide]

Patients enrolled in this study were of a wide range of ages. Again, slightly more than half were female,

primarily white. Most importantly, there was again a good balance between the two groups.

[Slide]

Once again, a wide range of organisms was encountered but the first top four species that we saw in study 373 also formed the basis of the microbiological analysis in study 433.

[Slide]

At the primary efficacy visit a statistically significant difference in clinical resolution in favor of besifloxacin compared with vehicle was observed in the culture confirmed study eyes.

[Slide]

A statistically significant difference in microbial eradication in favor of besifloxacin compared with its vehicle was observed at the primary visit on day five. That difference was maintained at visit 3, day eight, although treatment ended after five days.

[Slide]

Once again showing the broad-spectrum nature of the microbial eradication with besifloxacin, we saw very high species specific microbial eradication rates, and these

were independent of gram-stain characteristics.

[Slide]

In study 433 clinical resolution and microbial eradication were statistically significantly higher at visit 2 with besifloxacin treatment compared with its vehicle in meeting the primary endpoint. It is this study, along with study 373, that provides the confirmatory evidence of statistical superiority of besifloxacin over its vehicle. These studies were the pivotal efficacy data in the NDA.

[Slide]

The third large controlled safety and efficacy trial was study 434. Now, there are three important differences in this study compared with the previous studies. First, this study is an active comparator, moxifloxacin in the form of Vigamox, rather than the vehicle control.

The study used a non-inferiority analysis comparing both clinical resolution and microbial eradication rates of besifloxacin to those with Vigamox at the primary endpoint, visit 2. Like the previous study, two signs of bacterial conjunctivitis were used for evaluating resolution. Finally, in this study Asian sites

participated.

[Slide]

For the non-inferiority analysis 95 percent confidence intervals were constructed around the differences in the measured resolution rages. A non-inferiority limit of negative 15 percent for both efficacy endpoints was used to determine whether or not the non-inferiority endpoint was met.

[Slide]

This was the largest of the three studies. Approximately 1,200 patients were enrolled at 84 sites, 11 of those in Asia, and 46 percent of these patients had culture confirmed bacterial conjunctivitis.

[Slide]

Once again, we had patients with a wide range of ages involved in this study. Patients were still primarily females and white and again, as with the other two studies, the demographics were well balanced between the two groups.

[Slide]

Again, a wide range of organisms was encountered but the top four in this study were the same top four that were observed in the other two studies.

[Slide]

There were similar clinical resolution outcomes for the two active treatments. At both study visits clinical resolution with besifloxacin met the conditions of non-inferiority to Vigamox by having a lower bound to the confidence interval that was higher than negative 15 percent.

[Slide]

The two active treatments had similarly high rates of bacterial eradication. Importantly again, the lower bound of the confidence interval in both cases was well above the 15 percent, thus, meeting the non-inferiority conditions that were set forth.

[Slide]

As with the other studies, species specific eradication data indicated the broad-spectrum nature of besifloxacin. There were good eradication rates for the most frequently encountered organisms, including both gram-positive and gram-negative isolates.

[Slide]

Clinical resolution and microbial eradication observed at visit 2 following besifloxacin treatment were

non-inferior to those observed with Vigamox treatment, again satisfying the primary endpoints. Study 343 provides supportive efficacy data for the NDA, as well as pivotal microbiological and safety data for the integrated analysis.

[Slide]

So, I would now like to shift the focus of this presentation a little bit. Using an integrated analysis of the three studies I just discussed, I will show the clinical microbiological findings with besifloxacin treatment.

[Slide]

There were 1,324 isolates that formed the basis of this analysis. To nobody's surprise, the top four organisms are the same top four that were observed in each of the individual studies. Again, these organisms are quite consistent with expectations based upon the bacterial conjunctivitis literature.

[Slide]

This table demonstrates the improved potency of besifloxacin relative to other fluoroquinolones and antibiotics used to treat bacterial conjunctivitis today. With very few exceptions, you can see that the besifloxacin MIC-90s are better than or equal to the comparator drugs

tested against these isolates that were collected as part of our clinical program.

[Slide]

You see the same improved efficacy when looking at the multi-drug-resistant strains, in fact, in this case with no exceptions. So, besifloxacin MIC-90s are better than or equal to those that were measured with the comparator antibacterials.

[Slide]

So, in addition to evaluating activity against the resistant strains, as Dr. Morris alluded to during his presentation, we also did analyses to determine whether there were resistant strains emerging during our clinical trials. We found no evidence of any resistance emerging during these trials.

These analyses compare the MICs of besifloxacin and moxifloxacin for any genetically concordant organisms that were isolated at both baseline and at either follow-up visit from the same eye. There was no significant change in MICs for either drug. There was no emergence of resistance evident for besifloxacin within our trial and, furthermore, there were no organisms that developed resistance to another

fluoroquinolone as a result of exposure to besifloxacin.

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So, in conclusion, besifloxacin had superior outcomes versus its vehicle for both clinical resolution and microbial eradication in two separate clinical trials. Besifloxacin had a clinically equivalent outcome in the form of a successful non-inferiority trial when compared with Vigamox. We saw potent broad-spectrum eradication of both gram-negative and gram-positive organisms. Potent activity was also seen against resistant strains. Improved MIC-90s were measured versus competitive fluoroquinolones and other drugs used to treat bacterial conjunctivitis. We saw no evidence of resistance emerging during our clinical program.

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So, unless there are clarifying questions, at this point I would like to invite Dr. Schneider back to the podium to discuss the safety outcomes.

Safety and Conclusions

DR. SCHNEIDER: Good morning. My name is Susan Schneider, and I will be presenting the safety profile of besifloxacin ophthalmic suspension.

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Today I will discuss the clinical safety of besifloxacin by presenting results from three Phase 1 studies and an integrated analysis of results from Phase 2 and Phase 3 trials. This data represents trials conducted in healthy volunteers, as well as in patients with a clinical diagnosis of bacterial conjunctivitis.

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Let's first look at the Phase 1 besifloxacin safety studies. Clinical investigation of besifloxacin was initiated with study C-02-403-001 which was designed to evaluate the systemic safety, pharmacokinetics and ocular safety and tolerability of besifloxacin administered four times a day for one week.

This study demonstrated that in these healthy volunteers besifloxacin, 0.3 and 0.6 percent, was well tolerated and was assayed as vehicle. Results from this study led to further evaluation of besifloxacin in patients with conjunctivitis.

[Slide]

Study 478, also a Phase 1 trial, was initiated to evaluate besifloxacin's systemic pharmacokinetics and safety after a topical administration of the drug. In this study

24 patients with a clinical diagnosis of bilateral bacterial conjunctivitis received one drop three times a day for five days then a final single dose on day six. We saw that besifloxacin was safe with minimal systemic exposure in this population.

[Slide]

A third Phase 1 trial, study 507, was performed in healthy volunteers to assess potential corneal toxicity. There were 120 enrolled, 240 eyes. Volunteers received besifloxacin three times a day for five days in one eye. The fellow eye did not receive besifloxacin. Findings by specular microscopy were then compared to the fellow eye as well as to baseline.

We saw again that besifloxacin was safe and produced no significant change in corneal endothelial cell density. Therefor, the Phase 1 studies revealed that besifloxacin was safe and well tolerated.

[Slide]

Let's now turn our attention from the Phase 1 safety studies to the integrated analysis of safety in the Phase 2 and 3 trials. Studies 373, 433 and 434 were three large, well-controlled trials that represent the primary

safety population we will be presenting today.

[Slide]

In the integrated safety population patient age ranged from 10 months to 100 years, with a mean age of about 30 years across studies. The majority of patients were female and 70 percent of patients were white and this was balanced across treatment arms.

[Slide]

In looking at besifloxacin exposure, as shown here, we see the size of our safety database and the number of patients treated. There were 1,192 patients total in these three studies who received treatment with besifloxacin; 616 who received vehicle alone; and 579 who received treatment with Vigamox.

[Slide]

With the overall numbers and breakdown of treatment groups in mind, let's now look at the results of clinical safety from the integrated database of our key studies.

[Slide]

There were only four total serious adverse events reported during all three of these studies, and all reported

SAEs were considered unrelated to study drug. No deaths occurred in any study, and all SAEs were non-ocular. Specifically, there were two non-ocular SAEs reported in patients receiving besifloxacin, one SAE in a Vigamox-treated patient and one SAE in a vehicle-treated patient. SAEs were rare and sporadic across these three studies.

[Slide]

Overall, the incidence of treatment-emergent non-ocular adverse events was low, with 6.3 percent reported in those treated with besifloxacin. This compares with 7.8 percent in the vehicle-treated patients and 5.4 percent in the Vigamox-treated group. Most of the adverse events were mild and there were no imbalances observed among treatment groups.

Shown here are non-ocular AEs that occurred in greater than or equal to 0.5 percent. Notably, headache was the only non-ocular AE that occurred with a frequency of greater than or equal to 1 percent. This AE was reported in approximately 2 percent of patients and was balanced across treatment groups. Non-ocular adverse events were uncommon across these three studies.

[Slide]

There were no ocular serious adverse events reported in these three large, well-controlled trials. Overall, the incidence of ocular adverse events was low and most were consistent with the underlying ocular disease being studied.

Of note, when compared with the vehicle-treated group there were fewer ocular adverse events seen in the besifloxacin-treated group. The briefing document includes a list of all AEs that occurred with a frequency of greater than or equal to 0.5 percent.

Presented here are two corneal-related AEs that occurred in less than 1 percent of patients, punctate keratitis and corneal staining. These AEs were uncommon and it appears that besifloxacin does not adversely affect the corneal epithelium. Ocular adverse events were uncommon across these three studies.

[Slide]

Additional ocular safety assessments performed for studies 373, 433 and 434 were unremarkable. Visual acuity results across studies showed greater than or equal to 90 percent of eyes with 20/40 or better vision and no statistical difference between treatment groups.

Biomicroscopy revealed minimal findings across study arms, and these findings were consistent with the ocular condition being treated. Ophthalmoscopic examination revealed no treatment-emergent findings.

[Slide]

Another way to assess the clinical safety of besifloxacin is to examine the number of discontinued patients during these studies and the potential relationship, if any, to treatment. There were a total of 27 patient discontinuations from studies 373, 433 and 434 due to adverse events. Overall, the majority of associated adverse events were considered not treatment related. Those that were considered possibly related to treatment were uncommon.

Study discontinuations resulting from these adverse events were rare, and included only two besifloxacin-treated patients, one in study 433 for dermatitis and one in study 434 due to photophobia. By comparison, there were two Vigamox-treated patients who were discontinued from study 434 due to AEs and one in the vehicle arm in study 433.

[Slide]

To summarize, besifloxacin is safe and well tolerated. We have demonstrated that there is low systemic exposure associated with single and multiple doses of besifloxacin ophthalmic suspension. Treatment with besifloxacin had no effect on corneal endothelial cell density.

Overall, there was a low rate of reported adverse events. We saw no treatment-related serious adverse events. Non-ocular adverse events were infrequent. Ocular adverse events were also infrequent and were consistent with the underlying ocular disease being studied.

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We would like to now summarize our presentation and provide conclusions.

[Slide]

Based on the data we have presented to you today, we believe besifloxacin fits the ideal profile for the treatment of bacterial conjunctivitis. Besifloxacin provides broad-spectrum antibacterial therapy, with activity against a wide variety of ocular disease pathogens. Besifloxacin exhibits potent microbial eradication. It is bactericidal and has a low propensity for development of

resistance.

We have demonstrated excellent safety and tolerability in our target population. Besifloxacin ophthalmic suspension is administered with convenient dosing that is efficacious. The suspension has a long dwell time on the surface of the eye where the disease process is ongoing. And, besifloxacin is specifically designed to treat a local ocular disease.

[Slide]

Therefore, we conclude that besifloxacin ophthalmic suspension 0.6 percent is safe and effective in the treatment of bacterial conjunctivitis, and has a highly favorable benefit/risk profile to support this indication.

Now I would like to turn the podium over to Dr. Tim Comstock to take your questions. Thank you.

Questions/Clarifications

DR. REPKA: Thank you for those presentations. We will open the panel for questions. I will ask one which has to do with the data on patients 19 years and younger, which represent about a third of your sample. I don't know, perhaps from my lack of knowledge, whether the FDA has a rule on what constitutes the pediatric population, other

than age. But I wondered if there were data that differ from your overall data on the efficacy in that age range because, obviously, one of the big product areas, as you alluded to in the epidemiology, is that this would be applied to that population.

DR. COMSTOCK: So, we did do some analyses on the pediatric population with a finer discrimination between ages. We looked at the efficacy profile in patients younger than 2, 2-6, 7-12 and 13-19 years of age and saw very similar efficacy outcomes across those age ranges.

DR. AFSHARI: I have a question about the study C-2-403-001. How many days did normal volunteers take besifloxacin?

DR. COMSTOCK: Seven days.

DR. AFSHARI: Seven days? So, your data is consistent with the fact that besifloxacin is a potent antibiotic, and often potency comes with some corneal staining although some of the adverse events did not show that. But the question is in those studies, they were done for five days. The patients took it for five days. What is the maximum number of days that a patient or a healthy volunteer has taken besifloxacin, and then what was the

result in terms of the corneal staining?

DR. COMSTOCK: So, the maximum number of days was in the study that you first alluded to, the Phase 1 study in the healthy volunteers where we dosed four times daily, actually for seven days, and there were no reports in that study of any corneal surface adverse events.

DR. REPKA: Other questions? Dr. Levin?

DR. LAVIN: Yes, can you tell me if the patients self-administered this medication, or is it always administered in a controlled setting by someone else?

DR. COMSTOCK: In the efficacy trials it was self-administered by the patients.

DR. LAVIN: Okay. So, my next question then is what percentage of the patients misused the product in terms of, like, using it all up in the first day or so versus not using up enough of it, looking at the medicine when it is returned at the end of the study? Can you give some light on that?

DR. COMSTOCK: We monitored or characterized patient compliance with the dosing regimen in a couple of different ways. We gave patients worksheets that were used more to help them remember when to instill their drug and

record the time of that drug instillation. We also measured the weights of the bottles when they were dispensed and when they were returned. So, those are methods for estimating compliance. They are not methods that can be used to definitively say that the patient did everything right on every single day. But as far as the number of patients who were compliant based upon those estimates, it was quite high.

DR. LAVIN: How high would you say it was? Like, over 95 percent or what would you say compliance was on the high side and on the low side?

DR. COMSTOCK: I would probably estimate that it was on the high side maybe 90 percent, on the low side maybe 75, 80 percent. But those are really just kind of guesstimates.

DR. LAVIN: They tended to overuse or under-use?

DR. COMSTOCK: I think there was no overuse on a given day, but we had some patients who used them more than five days.

DR. LAVIN: Thank you.

DR. REPKA: Dr. Bilker?

DR. BILKER: I have a question about study 434.

You referred to it as a non-inferiority study but in the document it says that the FDA guidelines on what can be considered a non-inferiority study changed at some point, and that it was no longer a non-inferiority study. I just wanted a clarification on whether it really can be considered non-inferiority or not.

DR. COMSTOCK: So, maybe that wording wasn't quite right. It was still a non-inferiority study but the thinking at the FDA involved the use of non-inferiority studies for demonstration of efficacy. So, that is why we were advised to consider studies 373 and 433 the pivotal efficacy trials. But it was still a non-inferiority trial.

DR. BILKER: Thank you.

DR. REPKA: Miss Cofer?

MS. COFER: Hi. My question has to do with the adverse events that were seen with the besifloxacin-treated patients. Maybe it is in here and I missed it, but can you tell me if the adverse events resolved with discontinuation of the study drug?

DR. COMSTOCK: Any adverse event that was reported did resolve before the patients exited from the study so the answer would be yes, most of them resolved even while the

patients were still on treatment.

DR. REPKA: Dr. Miller?

DR. MILLER: I seem to recall that with the fluoroquinolones, on some of the labeling, they weren't approved in younger children because there were some concerns about joint cartilage growth, and there have been some reports of systemic medications more recently with some tendons actually rupturing.

My understanding is you have actually done a good job of looking at a pediatric group, better than some of the other studies I have seen in other committee meetings. But these are all healthy children with no joint development problems. You saw absolutely no indication of problems with growth or development? Nothing came up?

DR. COMSTOCK: That is right. Patients were in the studies for eight days, but in those eight days we saw no systemic adverse events that would be indicative of the kinds of things you are describing that have been reported in the literature for systemically administered fluoroquinolones. That is right.

DR. REPKA: Dr. Wilson?

DR. WILSON: From the last lecture on safety, I am

having problems interpreting one of the slides. I wonder if you can help me here, slide 14.

DR. COMSTOCK: We are bringing up that slide now.

[Slide]

DR. WILSON: Yes, that one. What is the difference between 0 and N/A, first of all?

DR. COMSTOCK: In study 373 Vigamox wasn't used and in study 433 vehicle wasn't used.

DR. WILSON: And I assume the parentheses are percentages?

DR. COMSTOCK: Correct.

DR. WILSON: So, are those right? I mean, that should be 0.9 instead of 1.9, shouldn't it if it is a percentage?

DR. COMSTOCK: It is probably the percentage from that study. It is study specific.

DR. WILSON: Oh, okay, got it. Thank you.

DR. REPKA: Let me ask about one issue. Early on Dr. Schneider mentioned that one of the goals of this treatment is reduced reinfection rates. Is there any data? At least, I don't see any presented that, in fact, that goal was attained in this particular project or with this

drug.

DR. COMSTOCK: So, we don't have data from our clinical program. That was more a general background kind of why ophthalmologists empirically treat bacterial conjunctivitis to try to prevent the contagious spread, but that wasn't a specific variable that was evaluated in this clinical program.

DR. REPKA: All right. Let's go over here. Dr. Gates?

DR. GATES: Are there any uses of this drug in veterinarian medicine?

DR. COMSTOCK: No.

DR. GATES: How about systemically?

DR. COMSTOCK: Nothing besides this formulation of bacterial conjunctivitis.

DR. GATES: Potentials?

DR. COMSTOCK: Anything I suppose is potential. At this point there is nothing planned.

DR. REPKA: Dr. Lavin?

DR. LAVIN: I have a question getting back to the efficacy data. I see that a lot of the same investigators participated in the three studies, your three pivotal

studies. I see a lot of consistency for microbial efficacy across the three studies for the besifloxacin but I don't see that for the clinical. Could you give me some insight as to why the numbers range from 33 percent in the first study to 45 in the second to 60 in the third? What would explain that from your understanding?

DR. COMSTOCK: So, the difference between the first two studies, 373 and 433, has mostly to do with the day of the visit. In 373 visit 2 took place on day four, versus 433 where there was an extra day of treatment and that visit took place on day five. The third study I think probably speaks to the FDA's evolved thinking on non-inferiority trials. We have observed that in active-controlled trials the clinical resolution rate seemed to go up for the same drug that is evaluated in a placebo-controlled trial.

DR. LAVIN: It is interesting. I hadn't really seen that type of thing before to that extent, and I was using your 33 percent, your day-adjusted in that first study, your 373 study. So, I was using your corrected number. But it still seems low and that is about the only thing that bothers me.

DR. COMSTOCK: I am sorry, I should probably

clarify. The adjustment for the first trial wasn't to adjust for the day; it was to adjust for the number of indices used to evaluate clinical resolution. So, the day we couldn't adjust because those patients were instructed to come back on day four.

DR. LAVIN: Did you ever do an analysis that actually looked at the data? Because you have a day window, plus/minus one day, so you have, like day three, day four, day five. Did you ever try to sort the data out to help you better understand that day factor?

DR. COMSTOCK: We looked at that data but the number of patients who returned on the target date versus the day after or the day before in the 433 trial was fairly low. So, in the 433 trial the number of patients who returned on day five or day six was actually quite a high percentage of the total number of patients. Unfortunately, we just didn't have enough patients who missed their visit window in the right direction in order to do that.

DR. REPKA: I have to ask one other question. Does the drug sting?

DR. COMSTOCK: Does the drug sting?

DR. REPKA: Yes.

DR. COMSTOCK: The rate of adverse events of stinging was very low.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: Is there a particular reason that the medicine is not a potential candidate for systemic treatment? Given that it has quite a good MIC-90, why not?

DR. COMSTOCK: Again, no particular reason. We are an ophthalmic company and we develop drugs for treating ophthalmic diseases.

DR. REPKA: Dr. Gates?

DR. GATES: What are the theories as to why so many patients in the placebo group improve? The natural history? BAK?

DR. COMSTOCK: It is a self-limiting condition so patients in the placebo group are going to improve. Some of it could be just a lavage effect from placing the drug in the eye and cleaning out the microorganisms. As you mentioned, the vehicle was preserved with BAK, as is the drug. So, BAK could have had an effect. All of those reasons are potentially contributing to that.

DR. REPKA: Other questions? Given that there are no other questions at this time, we will take a 15-minute

break. Panel members, please remember that there will be no discussion of the meting during the break amongst yourselves or with any member of the audience. We will resume at 9:30.

[Brief recess]

DR. REPKA: We will now proceed with our first presentation from the FDA. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Division of Anti-Infective and Ophthalmology Products: Advisory Committee Meeting for Besifloxacin Hydrochloride Ophthalmic Suspension for the Treatment of Bacterial Conjunctivitis

DR. NEVITT: Good morning.

[Slide]

I am Martin Nevitt with the FDA, the medical officer, and I will be presenting, from the FDA's perspective, besifloxacin hydrochloride ophthalmic suspension, 0.6 percent.

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The applicant, as you know, is Bausch & Lomb.

[Slide]

As far as the introduction and background, I just want to point out again that besifloxacin is a sterile topical ophthalmic suspension for ocular instillation. Also, it is an 8-chloro-fluoro-quinoline and this is a new molecular entity with an anti-infective activity.

[Slide]

The proposed indication is for the treatment of bacterial conjunctivitis, importantly, in subjects ages one and older dosed TID for seven days in the affected eyes.

[Slide]

As far as the drug information, again, this is besifloxacin and this will be a standard review because there are currently other drugs approved for bacterial conjunctivitis on the market. It is an anti-infective, fluoroquinolone and the dose administration is topical ophthalmic suspension.

[Slide]

As far as the basis to support safety and efficacy, there are three adequately controlled trials. The sponsor has mentioned them but I will go through them again, studies 373, 433 and 434. Importantly, 373 and 433 were superiority trials and study 434 was a non-inferiority

trial. Each study was conducted under similar but separate protocols. The sponsor has already outlined the differences and I won't go through those here.

[Slide]

Again, 373 and 433 compared besifloxacin with a vehicle, and these were superiority trials. Study 434 compared besifloxacin compared to moxifloxacin, and I will use moxifloxacin, not Vigamox, and this was a non-inferiority trial. In both trials the dose was three times a day for five days for the besifloxacin and the vehicle and moxifloxacin were dosed three times a day for five days.

[Slide]

As for the major inclusion criteria, I will go over them briefly. Again, it was ages 1 and older. I will point out that the scale of enrollment in the eye was based on 0 being complete absence of the sign and 3 being severe. In order to be enrolled you had to have a clinical diagnosis of acute bacterial conjunctivitis, and a minimal score of 1 for ocular discharge and 1 for injection. I won't go through the other inclusion criteria but they are listed there and I will leave them up for you to review.

[Slide]

As for major exclusion criteria, they were similar for all trials. If the patients had any uncontrolled systemic or debilitating disease they were excluded. I will point out that if they had an ophthalmic topical anti-inflammatory agent within 48 hours before and during study they were excluded. If they were likely to require antimicrobial therapy they would have been excluded. If they had known hypersensitivity to fluoroquinolones; if they were suspected of having viral allergic conjunctivitis or had a history of recurrent corneal erosion syndrome or active ulcerative keratitis they would also have been excluded. I will leave those up for you just to review quickly.

[Slide]

As far as the patient populations to look at the data, the safety/ITT population enrolled all patients who had at least one drop of the study medication. What I will refer to as the modified intent-to-treat population had at least one drop of the study medication and had baseline cultures indicating pathogenic bacterial levels. Finally, the per protocol population in essence are all your culture positive patients who did not have a major protocol

violation.

I do want to point out that in the per protocol population the subjects were identified during a masking approach. So, the sponsor wouldn't have known which patients were on which treatment when they pulled them out to perform just the per protocol population.

[Slide]

Overall, the safety and efficacy of this drug is based on studies 373, 433 and 434, and the total number of subjects enrolled was almost 1,200 in the besifloxacin group, a little over 600 in the vehicle group and approximately 500 in the moxifloxacin group.

[Slide]

As far as the demographics, as previously pointed out there were more females than males. I do want to point out that the sponsor did have a very good sample size even in the lower age groups, and there is a balance going from less than 2 years down to 1 year, all the way up to patients 60 and older.

[Slide]

As far as the primary efficacy variable, we looked at clinical resolution and we defined that as the absence of

the ocular discharge/injection. For microbial eradication efficacy was defined as the absence of ocular bacterial species that had been present at or above a certain threshold at baseline. The sponsor has gone over this previously.

[Slide]

As far as what the agency recommends for demonstration of efficacy, we are actually looking for statistically significant superiority in replicated studies to the product's vehicle in the cure in the signs and symptoms. Additionally, for the ITT population we want to make sure that the cure rate of the vehicle should not be numerically superior to the cure rate of the test product, and this is within the ITT population.

[Slide]

I will go through and start looking at these different populations that I will refer to as the ITT, MITT and, finally, the per protocol.

The efficacy endpoint for the ITTB-and these are all patients enrolled where they could have been culture positive or culture negative and looking at clinical resolution. This is study 373, besifloxacin compared to

vehicle.

Again, this is the study that had visit 3 on day eight as the preset clinical endpoint. When you compare besifloxacin to vehicle you see that the p value is significant and that the clinical resolution is 89 percent for besifloxacin versus vehicle. So, in this ITT population, in fact, the drug does beat the vehicle.

[Slide]

When we look at 433, again this is besifloxacin against vehicle, this study's endpoint was at visit 2 or day five and, again, you can see that the p value is significant. This p value is just to make sure there weren't any differences from the different centers. But I will really be focusing on the one that compares the treatments here.

Again, you can see that clinical resolution was 41 percent versus 33 percent in the vehicle, and this is at visit 2. Again, at visit 3, a little later on, it is still significant. The time period for this trial was actually set at visit 2.

[Slide]

Finally, this is the comparator trial where you

have besifloxacin compared to moxifloxacin. Again, the visit set was 2. Day five was the endpoint. You can see that these are similar, which is actually what we are looking for because what this is telling us is that besifloxacin is acting like moxifloxacin.

As we look at the clinical resolution, it is 55 percent versus 56 percent, and this is what we would hope would happen because moxifloxacin is currently on the market for this indication. So, besifloxacin is acting like moxifloxacin did in the clinical trial.

[Slide]

Now I am going to look at what I refer to as the modified intent-to-treat population, which are all your culture positive patients, and these are patients who had clinical resolution. Again, clinical resolution would be the absence of the injection and the other discharge.

For 373, again, this is slightly different and visit 3 was the preset time period. This is a little smaller sample size. The clinical resolution for besifloxacin is better than vehicle and it is clinically significant with a p value of 0.0058. Again, this is the culture positive patients.

[Slide]

Now we will look at 433. This is a larger sample size, one of the larger trials. This is, again, a superiority trial with culture positive clinical resolution. It is a little different. It was visit 2, day five. Besifloxacin compared to vehicle was statistically significant at 0.0354. If you just look at the clinical resolution rates you have 46 percent versus the vehicle at 35 percent.

[Slide]

Then, if you look at the comparator trial, 434, comparing besifloxacin and moxifloxacin at visit 2, you see that the clinical resolution is approximately 60 percent in both the approved drug as well as besifloxacin.

[Slide]

Finally, we looked at the per protocol population. The per protocol population has a little smaller sample size. This is 373 where besifloxacin is compared to vehicle and, again, this was at visit 3. They are not statistically significant in difference where the clinical resolution is 57 percent versus 42 percent. There is a trend for besifloxacin to have beaten the vehicle but the p value is

not significant and it might be attributed to the smaller sample size here.

[Slide]

As we look at the larger trial with the per protocol cases, there are a lot more patients in this trial, and also at visit 2 you have 151 versus 133. In the end, though they are not clinically significant at visit 2, we do see by visit 3 at day eight that there is a trend for clinical significance though, again, it did not reach that endpoint at this time though your clinical resolution rate just clinically at visit 3 is 87 percent versus 79 percent and at visit 2 it was 47 percent for besifloxacin versus 39 percent for vehicle.

[Slide]

Finally, if we look at the besifloxacin compared to moxifloxacin, the approved drug currently on the market, if we look at visit 2 we see that the clinical resolution rates are just about the same at around 60 percent, and at visit 3 they are about 90 percent.

[Slide]

As far as looking for bacterial eradication rates, this is eradication of all pathogens above a pathologic

threshold at baseline. In 373 the bacterial eradication rate is 90 percent versus 47 percent, and this trend continues at visit 3, being 88 percent versus 60 percent.

[Slide]

In 433, again, we have a much higher bacterial eradication rate, with besifloxacin versus the vehicle being 90 percent versus 60, and again about 90 versus 70, which would be expected and hoped for.

[Slide]

Finally for 434 again, the comparison trial of besifloxacin to moxifloxacin, you can see how the bacterial eradication rates are almost the same with 95 percent versus 90, and then at visit 3 it is 88 percent versus 85 percent for the comparator trial.

[Slide]

As far as what we look for, for the criteria for labeling in clinical microbiology, we look for bacterial eradication rate with greater than or equal to 50 percent eradication rate when you have greater than or equal to 10 cases identified. If you have 5-9 cases identified, we are looking for greater than or equal to 80 percent eradication rates.

If you only have 5-9 cases and you are successful in this group you will have an asterisk in the labeling. So, those organisms would be labeled as an asterisk. Also, if there are organisms cultured in less than 5 cases, they are not listed in the label.

[Slide]

This is those organisms which would qualify to be in the labeling. I am not going to read them all off. I would point out that there are a few with the asterisks and just remind you that those with an asterisk have the efficacy of this organism studied in fewer than 10 infections.

[Slide]

As far as the overall integrated review of the safety and efficacy, again, we looked at trials 373, 433 and 434 used to establish the safety and efficacy. I would like to point out again that all these trials were randomized, multicenter, double-masked and parallel-group.

[Slide]

As far as the disposition of the patients in the safety and the ITT population and looking just at the primary reason for discontinuation, you can see that it was

either withdrawn consent, loss to follow-up and lack of efficacy. I would like to point out that those who had lack of efficacy were primarily in the vehicle group. There were 7. In this other study it was 14. If you look at the besifloxacin group it is much fewer that would have dropouts due to lack of efficacy.

[Slide]

As far as serious adverse events in the clinical trials, as the sponsor pointed out, there were only four serious adverse events, one hospitalized for dehydration, one for pneumonia, one for congestive heart failure and there was one moxifloxacin subject hospitalized for a viral illness. There were no other serious adverse events reported and there were no deaths.

[Slide]

Overall, few adverse events were reported. As far as individual adverse events reported, they were all less than 2 percent, except for blurred vision which was 2.1 percent. Other frequently reported adverse events were eye pain, 1.8 percent; eye irritation, 1.4 percent; and eye pruritus, 1.1 percent. As far as non-ocular, headaches was approximately 2.1 percent. So, overall there were no

significant differences based on age, gender or race for safety or efficacy.

[Slide]

As far as postmarketing experience, as was previously brought up, besifloxacin is not marketed in any other country and, therefore, there are no other sources of adverse event information.

[Slide]

As far as questions for the panel, 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?

Finally, do you have any suggestions concerning the labeling of this product?

Questions/Clarifications

DR. REPKA: Thank you, Dr. Nevitt. We will open the floor to the panel for questions to Dr. Nevitt. Dr. Lavin?

DR. LAVIN: Yes, I have a question regarding this general drug class. As a statistician, I don't know a lot

about it but perhaps the FDA could share a sense for the safety experience of other products in that drug class and just give an insight for the risks here.

DR. NEVITT: Well, as far as when you look at the risks for this drug they are very small. They are all in the less than two percent range.

[Slide]

In the moxifloxacin group, this is the primary reason for discontinuation and there were five patients who discontinued for adverse events, and for the besifloxacin group it was similar considering there is a larger sample size.

I don't have a slide here but there is a slide that the sponsor showed, not here but in the review, where you have the besifloxacin compared to moxifloxacin and you don't see any difference in the adverse event rates in the moxifloxacin group versus the besifloxacin, at least in this clinical trial.

DR. LAVIN: And how long has moxifloxacin been available and what is the number of units, of patients and doses administered for that? How long has that been on the market? Just so that I have a sense of comparison.

DR. NEVITT: I don't know exactly. Dr. Chambers might know how long moxifloxacin has been on the market.

DR. CHAMBERS: Wiley Chambers. The first of the fluoroquinolones for ophthalmic use were approved approximately in the 1989-90 kind of time frame. At that point the first series of them came out on the market and that was cipro, norflox and ofloxacin. So, they have been marketed for approximately the last 18 years or so. The next generation included moxifloxacin and I don't remember the exact year but I would say it is probably six or seven years ago.

Each of these all have systemic versions, though there have been some issues. In fact, the issues with arthropathy in developing children were identified before the first generation of fluoroquinolones, as Dr. Miller was pointing out. The systemic level that is achieved with any of the ophthalmics is well below what has ever been shown in any animal models to cause any of the particular problems that have been seen with the systemic products.

DR. LAVIN: So, this drug tracks preclinically like those others did?

DR. CHAMBERS: That is correct.

DR. REPKA? Miss Cofer?

MS. COFER: Will we have an opportunity to give suggestions for the labeling after the open public hearing or would we do that now? Or questions or suggestions for the labeling?

DR. REPKA: Normally, we would do it after the public hearing and I think we will do it then.

Dr. Nevitt, I wondered if you would comment on what your thoughts are on this ten percent superiority limit that we saw in this project as an efficacy endpoint. Is that one that we should be looking at seriously, or is it so small as to not be worthwhile?

DR. NEVITT: I think you are referring to the non-inferiority margin of 15 percent.

DR. REPKA: No, actually to the superiority trial over vehicle where we were I think seeing just ten percent in the all patients treated program, which is how this drug will be administered to the public.

[Slide]

DR. NEVITT: This is the study you are talking about, the ITT population for these trials, not necessarily culture positive.

DR. REPKA: Yes.

DR. NEVITT: Well, we really want to make sure that the vehicle group doesn't have a better result than besifloxacin. Probably what you are concerned about, as you are mentioning, is that when patients come into the office you are not going to know if they have viral conjunctivitis or bacterial conjunctivitis. So, therefore, you are going to treat all-comers. This will show you that we know that vehicle loses to the drug. So, the drug is not potentiating the viral components that the patient may have.

If you did have a way to differentiate the viral component from the bacterial component, then you wouldn't necessarily have to use the ITT. You could just use the culture positive. But since in clinical practice you don't have any way to really define who has viral conjunctivitis initially versus bacterial you are going to treat everyone.

So, based on this, I feel quite confident that, you know, the drug is beating the vehicle as well as not potentiating the effects of a viral conjunctivitis.

DR. REPKA: Let me ask you if you could pull study 433 for the same question.

[Slide]

DR. NEVITT: At visit 2 it was statistically significant. You also have to realize that visit 3 which is, you know, getting closer to the clinical resolution is the same but your sample size is fairly large here and does show a p value that is clinically significant.

DR. REPKA: It actually shows a p value that is statistically significant. Actually, I was asking the question, perhaps for the clinicians on the panel, is that a clinically significant benefit compared to vehicle.

DR. NEVITT: I also want to point out that at day eight you are starting to get to where this is a self-limiting disease so, therefore, you know, you may want to look more at visit 2 to see if it is there. In other words, the disease is running for a shorter period of time.

I would expect it is harder for this drug to win against vehicle as you get further out in the time frame, like day eight or if you go to day 12, or something like that.

DR. CHAMBERS: Dr. Repka, are you asking for what historically the things are, or explanations for why they are close? We can give you either one.

DR. REPKA: Actually, I am probably asking more

philosophically, Wiley, about what we and sponsors should be striving for on this kind of margin over vehicle.

DR. CHAMBERS: The issue has always been how much of a difference you are potentially going to show, and how do you do that in a controlled environment. The bacterial conjunctivitis trials we have done as masked trials and so tried to have a vehicle that was matching it. Vehicle is required by regulation, because it is a multi-dose product, to have a preservative in it.

So, we have asked people to literally use the vehicle that is going to be marketed and those tend to have benzochromium chloride, as this one does. Benzochromium chloride is a preservative in there because it is a very effective killer. In addition, we are putting drops in which wash the bacteria out.

So, we call it a placebo; we call it a vehicle. It is not innocuous. It is killing bacteria and it is washing things out, the same as the product. So, what you are seeing is what is the additional effect of the anti-infective component, or you would say, well, why don't we just give vehicle to everybody? If you were to give the vehicle to everybody you are going to get these types of

cure rates. I mean, you are going to get a relatively large percent that just the vehicle is capable of treating. What you are not getting is that extra benefit along there, and the question is always what is the extra risk associated with that extra benefit.

We can show you a table of what other product, have done in the past. Typically, you are talking about 10-15 percent difference over vehicle for all the products, you know, cipro, norflox, oflox, levo, you name the product and they have all run 10-15 percent better compared to vehicle during the clinical trials that match this.

DR. REPKA: And, another way of answering my question is that this is a margin we could expect to see, not anything larger. Has anything ever been done looking at balanced salt solution compared to vehicle compared to drug with vehicle?

DR. CHAMBERS: We have not tended to do anything that did not have the preservative in it. It is certainly possible to do, but you have to go to a different configuration where you are either doing one drop out of each bottle or you are doing small container bottles in packaging it and, because of the subjectivity that is

involved, you heard some mention before that if you do an active-controlled trial the rates always end up being a little higher than if you do a vehicle-controlled trial. That has been consistent for the past at least 20 years that I have been involved in doing this.

So, we try to do the best we can to minimize the potential bias. It is certainly possible to do, but you are still going to have a washing out effect even if you don't have the preservative effect. If you do these MIC curves, and things, with the benzochromium chloride, it is an effective killer.

DR. REPKA: Dr. Miller?

DR. MILLER: Speaking of which, what color is the besifloxacin? Because Vigamox is fairly obviously yellowish in color.

DR. NEVITT: I will let the sponsor answer it. I actually haven't seen the color.

DR. MILLER: I am curious.

DR. COMSTOCK: Our formulation is slightly differently colored than the Vigamox. The way that we addressed that as far as masking is we didn't allow the drug to be instilled in the presence of the investigator.

DR. MILLER: Thank you.

DR. REPKA: Dr. Wilson?

DR. WILSON: Again, this is a general question and not specific to the study, but in the non-inferiority trials I think it was minus 15 percent. That seems like it was pretty lenient. Has that been a change recently or has that been pretty standard?

DR. NEVITT: I will let Wiley respond to that.

DR. CHAMBERS: Historically, this was last discussed at an advisory committee meeting in 1990. Although we invited some of the same people that were at that meeting, for various conflicts and things, we don't have anybody here that was here at the time, beside myself.

The issue has been, as you have heard many times before, trying to decide on a non-inferiority margin. The superiority that you see is relatively small. You see this 10-15 percent. So, it has been reproducible but for any single trial, if you were to base a non-inferiority margin on what you could rule out as far as making sure that you weren't fooled into thinking that you had equal efficacy, if you based it on the numbers from a single trial it would require 12,000 patients to show a non-inferiority margin of

approximately two percent.

So, if you take this ten percent, and there are margins around that which drop you to about five or six percent, and if you were to preserve half of that margin you get down to two percent. So, you would really want to show that you were within two percent if you were following our standard rules based on a single trial.

If you couple multiple different vehicle-controlled trials and were just slowly accumulating multiple trialsB-we have about six or sevenB-you probably could change that margin for non-inferiority and bring it up to five or six percent. I am not sure exactly where because we haven't put them all together.

But the feeling has been that the best evidence is showing superiority over vehicle. When we discussed this in 1990 and presented people with, okay, you can do a non-inferiority trial and it would require 12,000 patients to do, people said, well, that is not ever going to lead us to any kind of ophthalmic development of anti-infective products. Nobody is going to study things in 12,000 patients. We don't really need that kind of safety database. We don't need to be that close.

So, we set up at the time what was a sliding scale. The sliding scale said that if the efficacy of the comparator were 90 percent or better, we wanted it within 10 percent. If we were between 10 and 20 percent, we would take 100 minus whatever that number is. So, if the success was 85 percent we would say 100 minus 85 and say 15 percent. We wanted it to be within 15 percent. If we were 80 percent or below we would take 20 percent.

As you can see and as you have heard, where you are in that percentage depends on what day you go and measure. If you go and measure early on you get rates that are below 80 percent. If you start measuring things on day eight, seven, nine kinds of times, you get things that are closer to 90. You can literally just set that along there.

In the last couple of years where there have been more discussions about non-inferiority margins our statistical colleagues have not liked the sliding scale. Because you didn't know what it was up front, it was difficult to plan how many patients you needed because you didn't know what the results were going to be and you didn't know what the target was going to be. You knew how to figure out the target but you didn't know what it was going

to be.

So, we literally took the middle number. We took the 15 percent for particular things and it doesn't come from anything more scientific than having taken the middle of the 10 and the 20.

If you truly want a tight margin based on one study, it is two percent and that is why you see it not being used as the primary support for these trialsB-we have two other vehicle-controlled trials; why even get into that if we don't need to?

At some point we may decide we want to not continue to do vehicle-controlled trials. We did not in this trial, but in the previous product we approved, the azithromycin, in the vehicle arm we had a corneal ulcer. Yes, it had the same 10-15 percent range of superiority but, as you know, there is the risk, if there is a small percentage that you don't go and treat and the bacterial infection continues, that some of them will do poorly. And, we had one patient in the vehicle-controlled trial that had a corneal ulcer.

How many trials do you want to continue to run where you put people at potential risk, although small? I

mean, you saw 600 or 700 patients done through this trial and nobody had a corneal ulcer that I am aware of. So, it is not a very high risk. These people are being monitored closely along and so, if they get into trouble, they will quickly be rescued. But it is a potential risk.

But the alternative at the moment is to do a trialB-I am willing to hear suggestions. If you think we should be running 12,000 patient trials, by all means tell us. But the other alternative is that these are the types of results you get. So, that is probably a longer answer than you necessarily wanted but that is a more complete history.

DR. REPKA: Dr. Lavin?

DR. LAVIN: I want to make a comment on that because I think Dr. Chambers was basically about 18 years ahead of his time in trying to avoid people doing 12,000 patient studies. I think the data here--and part of the reason that this panel was convened, was to try to put into context the results of study 434 where, at the microbial level, we are ruling out as a lower 97.5 percent one-sided interval 2.44 percent.

So, that, to me, would be consistent with the kind

of numbers that Dr. Chambers was alluding to. Also, if you look at day eight you are ruling out a 3.3 percent. And, that is at the microbial endpoint. For the clinical resolution you are ruling out 10 percent and you are ruling out 5.6 percent.

So, I think we are coming close to those numbers practically, and so I think that the position of our group, of our panel, is to judge whether or not that study really does constitute a demonstration of non-inferiority in a practical sense or a clinical sense. Statistically, it is a matter of the offset that is accepted and you, as clinicians, have to judge whether that is acceptable.

DR. REPKA: Thank you. Other questions or comments? Dr. Bilker?

DR. BILKER: I agree with you, Dr. Chambers, in terms of the sample size. It is not possible to do 12,000 people. But I just wanted to make one point, and that is that the non-inferiority margin is 15 percent but the difference between the vehicle and the drug is 10 percent. So, you have that difference being less than what you are calling superiority.

DR. CHAMBERS: Without question. I mean, it is

running at the same margin that we are talking about. As I don't need to explain to you and probably the rest of the group, these are the 95 percent confidence intervals. They are not the point estimates. The point estimates, obviously, are much closer to there. But if you truly want to rule it out we typically use 95 percent confidence intervals, and the 95 percent confidence intervals are wider.

As the sponsor pointed out, we did give them advice to follow what the advisory committee said. The advisory committee in 1990 told us to run one vehicle-controlled trial and run one active-controlled trial so we can see where it stands. We know that the rates are going to be a little bit behind there.

But we wanted to get more safety information. We wanted to get a comparison to another ophthalmic product that is on the market because the clinicians wanted to have that kind of comparison. They knew they would have a clinical feel for an active comparison and they wanted to be able to rate where it stood with one of the currently approved products. So, it was a compromise, knowing that you would be able to see the efficacy out of one of the

trials and not necessarily out of the other.

The thing that has been modified since that time is that we have said we will take just one vehicle-controlled trial if the product is systemically approved, not necessarily systemically but approved for another indication.

If we know that there is an approval for killing bacteria for some other site in the body, we know that there is a prior assumption that it does work, not necessarily in the ophthalmic formulation, not necessarily for this vehicle or not necessarily for this formulation but we can be convinced with essentially the replication being a second trial in the ophthalmic indication we are interested in. So, we asked for one vehicle-controlled trial and then this comparator to something that won't necessarily rule out a vehicle.

This product does not, as you have heard, have a systemic formulation or systemic indication, or it is not approved in anything else. So, for here we rely back on having two vehicle-controlled trials, and that is why you are hearing the issues with having two vehicle-controlled trials here instead of what has been one vehicle-controlled

trial and one active control as the primary basis.

DR. REPKA: Thank you, Dr. Chambers. Seeing as there are no other questions, I think we will move to a ten-minute break. Panel members, please remember that there should be no discussion of the meeting during the break amongst yourselves or with any member of the audience. We will resume at 10:20

[Brief recess]

Panel Discussion/Questions

DR. REPKA: Thank you for returning on time. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure that transparency at an open public hearing session of the advisory committee meeting was made available to the public was in the Federal Register. There were no applications to present at the open public hearing so we won't be having an open public hearing this morning on this application.

So, we are going to then move back to panel deliberations regarding the specific questions before us today. So, we will now begin the panel discussion of the meeting. Although this portion is open to public observers,

public attendees may not participate except at the specific request of the panel.

The first question that is brought to our attention is on the image. It is question 1. For besifloxacin ophthalmic suspension, do you think the benefits outweigh the risks for the treatment of bacterial conjunctivitis?

The voting members of the panel will be voting on this at the conclusion of the discussion. So, I would like to open the floor for discussion of this question simply related to this vote.

It would appear that the panel has exhausted their questions to the specific speakers, fortunately. Yvette, do you want to go through the voting procedures or can I manage?

DR. WAPLES: I think you can manage.

DR. REPKA: Thank you. So, there is a yes or no vote button and an abstention button. There is a time limited period to vote. It should illuminate and then you just push yes or no if you are a voting panelist.

[Electronic voting]

DR. REPKA: The tabulation for voting on question

1, yes, 9; no, zero; abstain, zero.

DR. WAPLES: Before we move on to question 2, for the record we need everyone to go around the table and state their name and their vote, just to record into the tape. Thank you.

DR. CHAMBERS: Also, preferably why they voted the way they did vote, please.

DR. WAPLES: Yes, thank you, and explain your vote.

DR. REPKA: So, Dr. Afshari?

DR. AFSHARI: My vote was yes. Natalie Afshari, from Duke University. The reason was the clinical data and the wide spectrum of the coverage of the antibiotic.

DR. REPKA: Dr. Bilker?

DR. BILKER: Warren Bilker, from University of Pennsylvania. I voted yes, and it is because of the efficacy and safety profile for this medication.

DR. REPKA: Miss Cofer?

MS. COFER: I voted yes. The clinical trials seemed to prove the drug is safe and effective, and minimal adverse events.

DR. REPKA: Dr. Gates?

DR. GATES: William Gates. I voted yes. I was

very satisfied with the statistical breakdown for safety and efficacy.

DR. REPKA: Dr. Lavin?

DR. LAVIN: I voted yes, my reasoning being that the product demonstrates safety in every respect, and also demonstrates efficacy both at the microbial level as well as the clinical level. The data at the microbial level tie together and also go down to the original organisms. So, I find it very comforting.

DR. REPKA: Dr. Majumder?

DR. MAJUMDER: Mary Majumder, from Baylor College of Medicine. I voted yes for the reasons already stated. Safety and efficacy appear to have been established.

DR. REPKA: Dr. Miller?

DR. MILLER: Dr. Marijean Miller. I agree that the safety and efficacy was shown by the data presented, and also there is clearly increase in different bacterial pathogens and we need to have more medications, and I thought that the non-inferiority was proven to my satisfaction.

DR. REPKA: Dr. Repka. I similarly agree with the previous panelists that the efficacy data was sound and that

the age range data looked quite good, and certainly reassuring to me as a pediatric ophthalmologist to the value of this kind of treatment. Dr. Wilson?

DR. WILSON: I voted yes. The efficacy and safety profile either met or exceeded the standard that has been established.

DR. REPKA: Thank you. Actually, we will skip question 2 as it is not pertinent to the discussion. Question 3, do you, the panel, have any suggestions concerning the labeling of the product? Miss Cofer, I believe you had one earlier.

MS. COFER: Paula Cofer. My question is in the labeling how will the issue of preexisting dry eye be handled. Will that be a contraindication for the drug, or some warning in the labeling?

DR. REPKA: Was there anything you saw in the data that worried you on that issue?

MS. COFER: I did see some issues related to dry eye in the adverse events in the besifloxacin-treated patients.

DR. CHAMBERS: Can you be a bit more specific about which events?

MS. COFER: Let me back up. In the contraindications for the clinical trials it did list dry eye andB-what was the other one?

DR. CHAMBERS: For the exclusion criteria?

MS. GOFER: Yes, for the exclusion criteria. Correct.

DR. CHAMBERS: And the reason that is typically done is so that we don't confuse a red eye as being from dry eye and that we know they really have bacterial conjunctivitis, not because there is necessarily any interference with dry eye. We are trying to get people to really have the diagnosis of bacterial conjunctivitis.

I am just trying to think in general if we didn't exclude themB-I am putting words in your mouth but I am assuming that you are concerned that there were not enough people studied with dry eye for them to go and use it. I am not sure I would want to deprive people with dry eye of this product unless there was a good reason to do it.

DR. REPKA: Dr. Strahlman, you have some comment?

DR. STRAHLMAN: Yes. Perhaps FDA could comment on the large experience of this class of compounds with regard to safety and dry eye, if any, to give a context around this

discussion.

DR. CHAMBERS: This is Wiley Chambers. I am not aware of any interactions with dry eye or any particular problems with dry eye patients using any of the fluoroquinolones. I mean, we will go back and look at adverse events reported with them, but I am not aware of any particular interaction or any particular problem. We certainly have expertise on the panel and you can ask if they have seen anything with any of the other fluoroquinolones.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: I agree with Dr. Chambers that we see a wide variety of patients with dry eyes and it is not a contraindication, or hasn't been. Yet, I also understand that it would be one of the points of exclusion because sometimes the dry eye patients have irritation. It would be hard to tease out redness or irritation which waxes and wanes. Could it be from the new medicine versus their dryness, you know, becoming worse at times?

DR. REPKA: Dr. Lavin?

DR. LAVIN: My sense would be that this would follow the moxifloxacin labeling, unless I would hear

otherwise.

DR. REPKA: Other comments, first on the dry issue or corneal surface issue, then on other issues on labeling? Seeing none, and there are no other issues, we have completed the questions for the committee.

DR. CHAMBERS: I do want to thank the committee. We may have gone through this relatively quickly. I do want everybody to understand we do appreciate that there is background time before you get here for going through and looking at things, and we do thank you very much for spending the time to go and do that, and for your deliberation this morning. Thank you.

DR. REPKA: This room is apparently secured during lunch. The panel is to remember to have no discussion outside of the meeting. We will now break for lunch and reconvene at 11:45. Please take any personal belongings you may want with you at this time. The ballroom will be secured by FDA staff during the lunch break and you will not be allowed back in the room until we reconvene. Panel members, please remember that there should be no discussion of the meeting at lunch amongst yourselves or with any member of the audience. Thank you. Once again, 11:45.

[Whereupon, at 10:30 a.m. the proceedings were recessed for lunch, to reconvene at 11:45 a.m.]